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0410

Docket No.: CI-0001

PATENT 1/22/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	**OFFICIAL DRAFTSMAN**
Wilson BURGESS, William N. DROHAN, Martin J. MACPHEE, David M. MANN and Ewa MADDOX	Group Art Unit: 1744
Serial No.: 09/925,619	
Confirm. No.: 2963	
Filed: August 10, 2001	
For: METHODS FOR STERILIZING BIOLOGICAL MATERIALS USING DIPEPTIDE STABILIZERS	

#7

8/29/02
D.D.

LETTER SUBMITTING FORMAL DRAWINGS

Assistant Commissioner for Patents
Washington, D. C. 20231

Sir:

Submitted herewith are 31 sheets of formal drawings (Figures 1A-1C, 2A-2E, 3A-3F, 4A-4C, 5A-5B, 7-14 and black and white photographs for Figures 3G, 3H, 6A and 6B) in connection with the above-identified application.

Respectfully submitted,
FLESHNER & KIM, LLP

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703 502-9440 MLF:DRM:kpc
Date: January 23, 2002

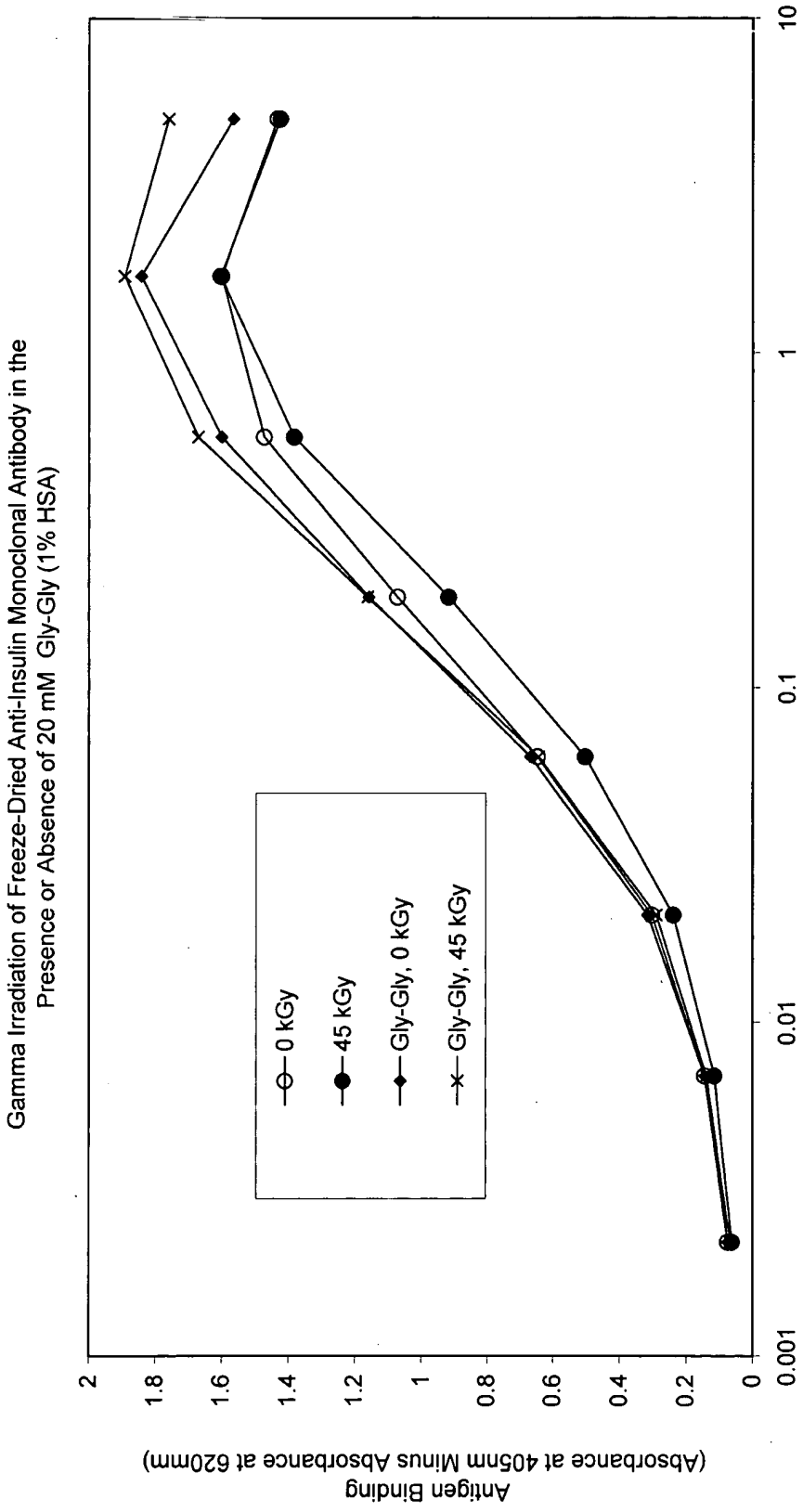
Gamma Irradiation of Freeze-Dried Anti-Insulin Monoclonal Antibody in the Presence or Absence of 20 mM Gly-Gly (1% HSA)
Antigen Binding (Absorbance at 405nm Minus Absorbance at 620nm)
Concentration of Anti-Ig Lambda Light Chain (µg/ml)
0 kGy
45 kGy
Gly-Gly, 0 kGy
Gly-Gly, 45 kGy
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
2
0.001
0.01
0.1
1
10

FIG. 1A

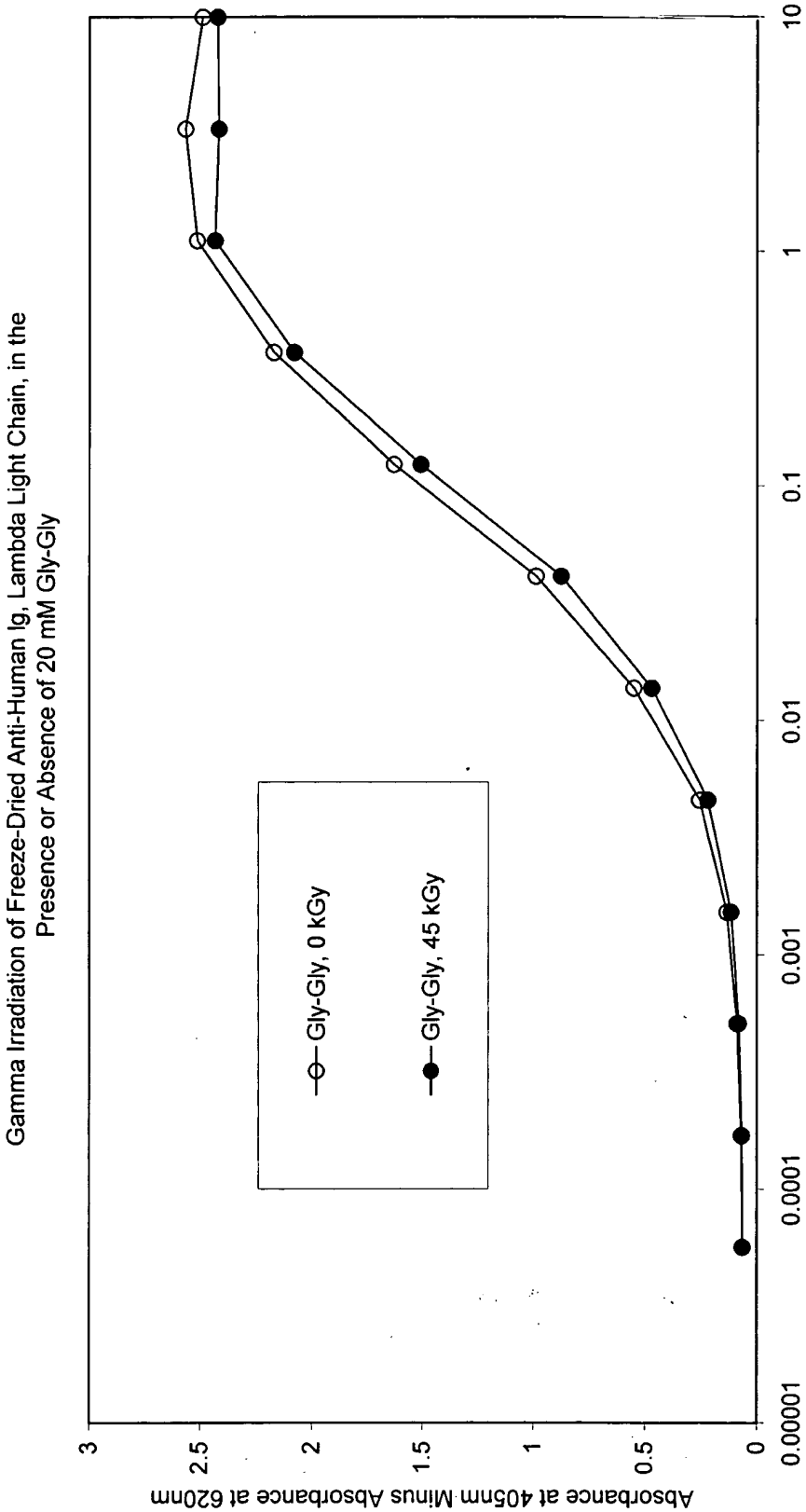
Gamma Irradiation of Freeze-Dried Anti-Human Ig, Lambda Light Chain, in the Presence or Absence of 20 mM Gly-Gly
Absorbance at 405nm Minus Absorbance at 620nm
Concentration of Anti-Ig Lambda Light Chain (µg/ml)
Gly-Gly, 0 kGy
Gly-Gly, 45 kGy
0
0.5
1
1.5
2
2.5
3
0.00001
0.0001
0.001
0.01
0.1
1
10

FIG. 1B

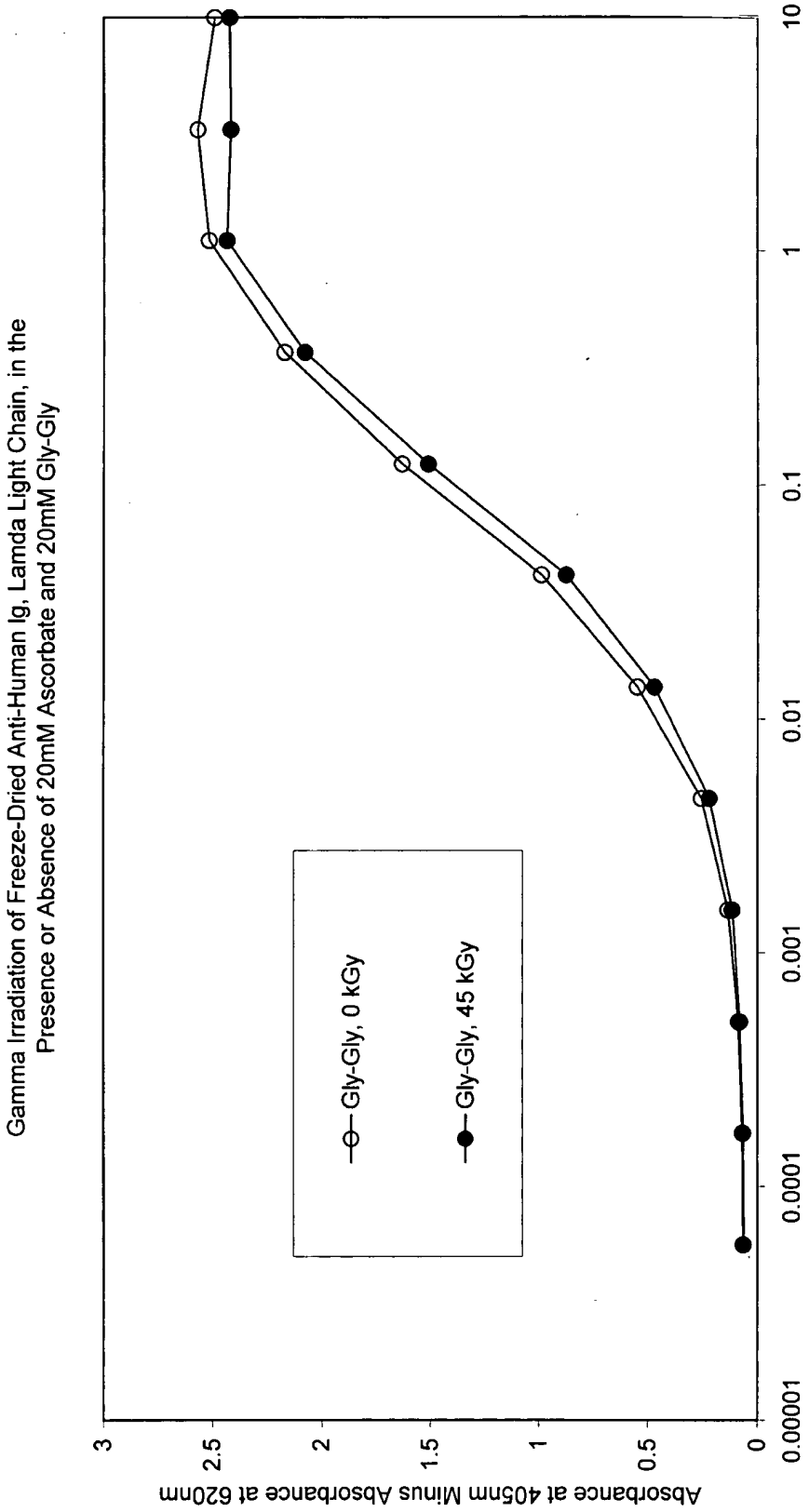
Gamma Irradiation of Freeze-Dried Anti-Human Ig, Lamda Light Chain, in the Presence or Absence of 20mM Ascorbate and 20mM Gly-Gly
Absorbance at 405nm Minus Absorbance at 620nm
Concentration of Anti-Ig Lambda Light Chain (µg/ml)
Gly-Gly, 0 kGy
Gly-Gly, 45 kGy
0
0.5
1
1.5
2
2.5
3
0.00001
0.0001
0.001
0.01
0.1
1
10

FIG. 1C

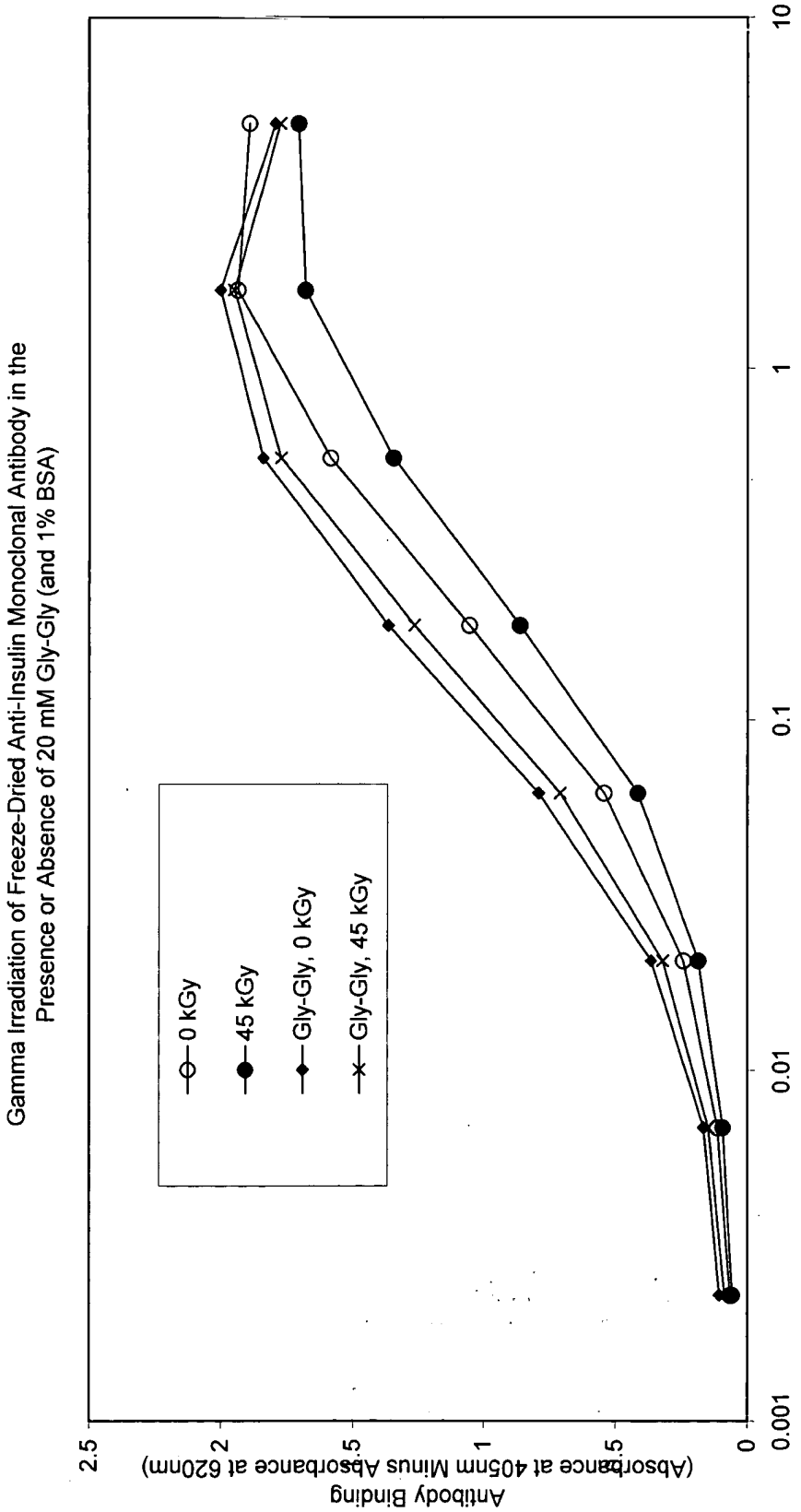
Gamma Irradiation of Freeze-Dried Anti-Insulin Monoclonal Antibody in the Presence or Absence of 20 mM Gly-Gly (and 1% BSA)
Antibody Binding (Absorbance at 405nm Minus Absorbance at 620nm)
2.5
2
1.5
1
0.5
0
0.001
0.01
0.1
1
10
(µg/ml)
0 kGy
45 kGy
Gly-Gly, 0 kGy
Gly-Gly, 45 kGy

FIG. 2A

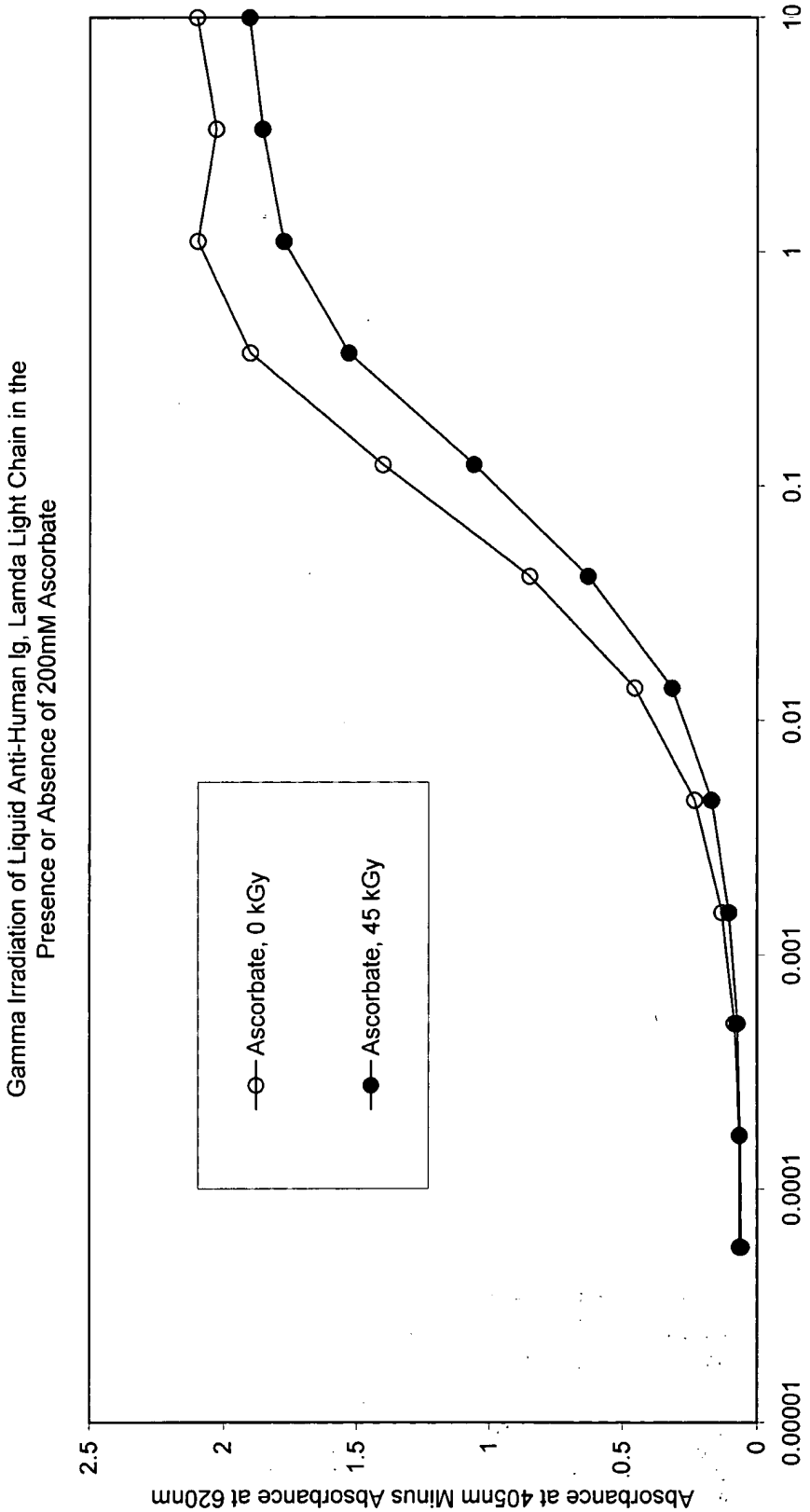
Gamma Irradiation of Liquid Anti-Human Ig, Lamda Light Chain in the Presence or Absence of 200mM Ascorbate
Ascorbate, 0 kGy
Ascorbate, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm
2.5
2
1.5
1
0.5
0
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration of Anti-Ig Lambda Light Chain (µg/ml)

FIG. 2B

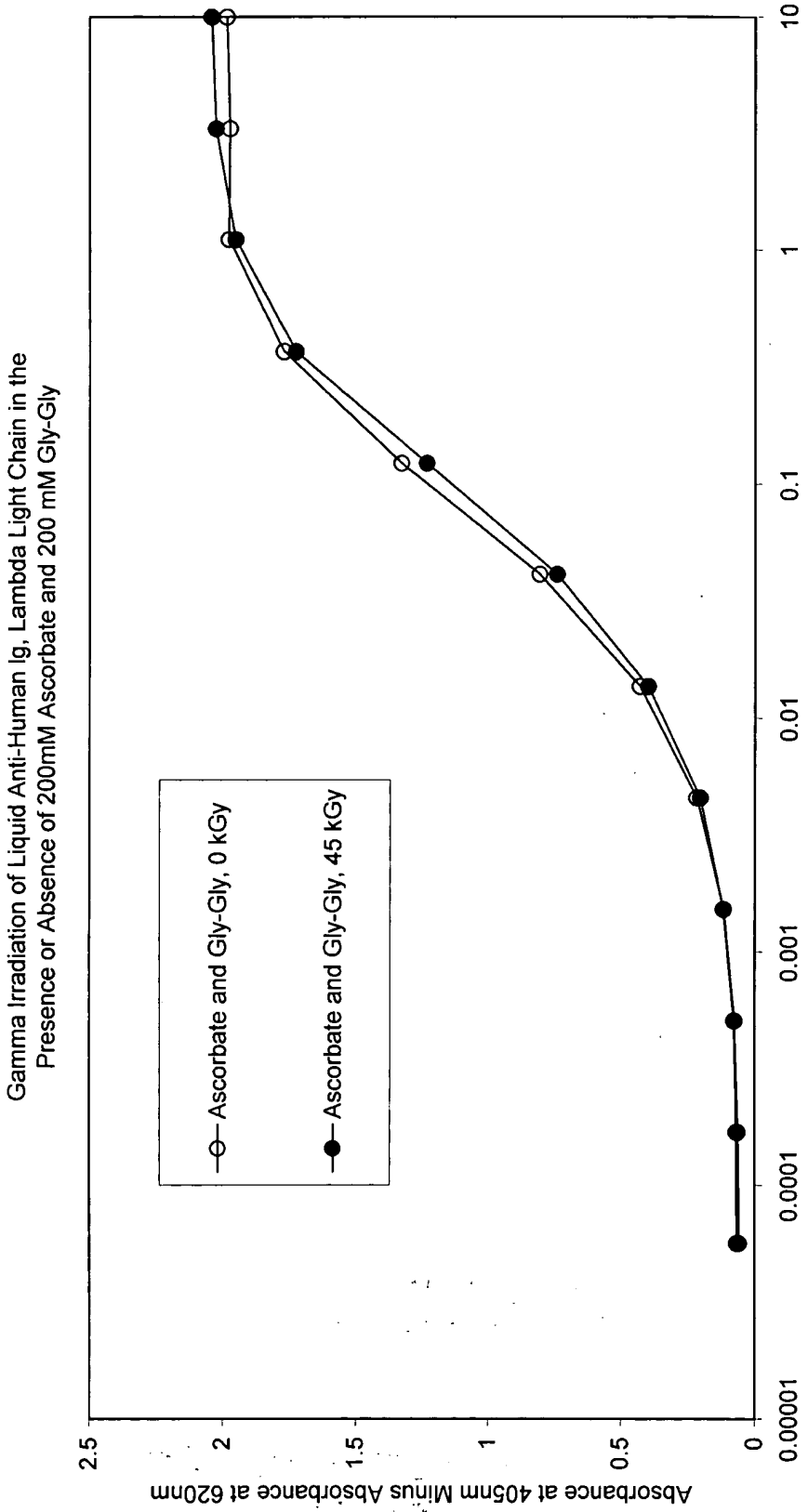
Gamma Irradiation of Liquid Anti-Human Ig, Lambda Light Chain in the Presence or Absence of 200mM Ascorbate and 200 mM Gly-Gly
Absorbance at 405nm Minus Absorbance at 620nm
2.5
2
1.5
1
0.5
0
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration of Anti-Ig Lambda Light Chain (µg/ml)
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 45 kGy

FIG. 2C

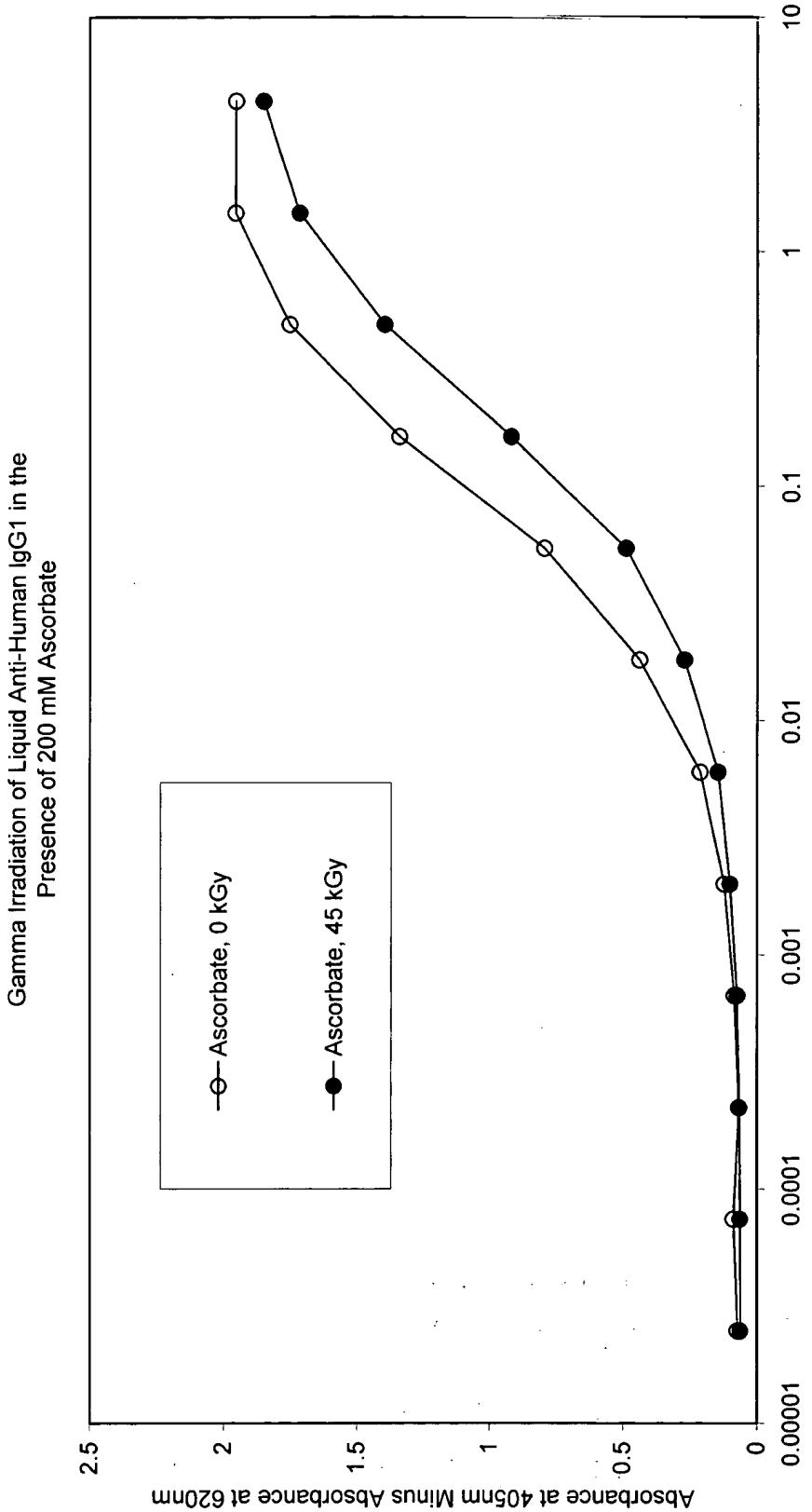
Gamma Irradiation of Liquid Anti-Human IgG1 in the Presence of 200 mM Ascorbate
Ascorbate, 0 kGy
Ascorbate, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm
2.5
2
1.5
1
0.5
0
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration of Anti-Human IgG1 (µg/ml)

FIG. 2D

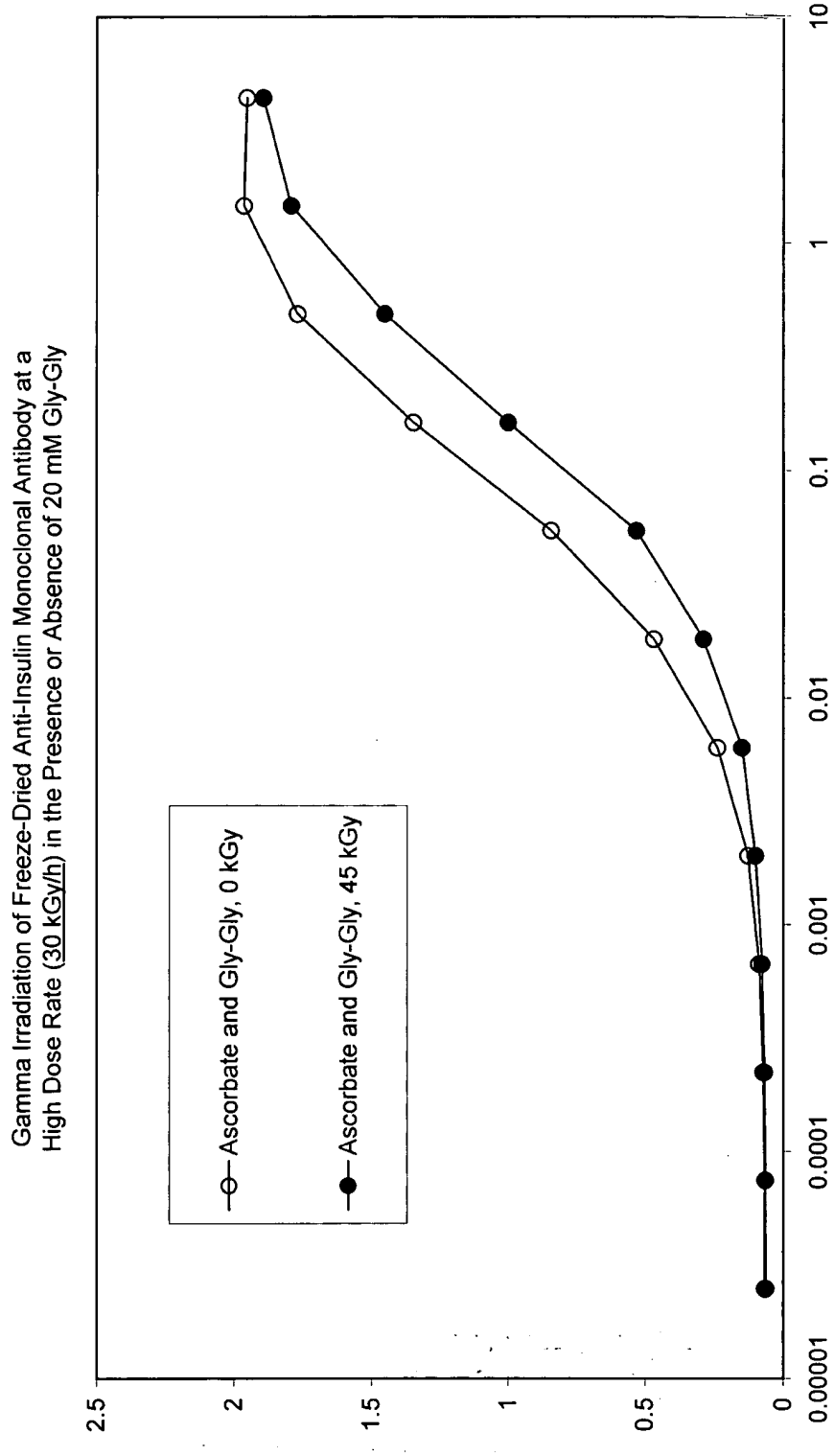
Gamma Irradiation of Freeze-Dried Anti-Insulin Monoclonal Antibody at a
High Dose Rate (30 kGy/h) in the Presence or Absence of 20 mM Gly-Gly
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 45 kGy
ANTIGEN BINDING
(Absorbance at 405nm Minus Absorbance at 620nm)
2.5
2
1.5
1
0.5
0
0.00001
0.0001
0.001
0.01
0.1
1
10
Concentration of Anti-Insulin Monoclonal Antibody
(µg/ml)

FIG. 2E

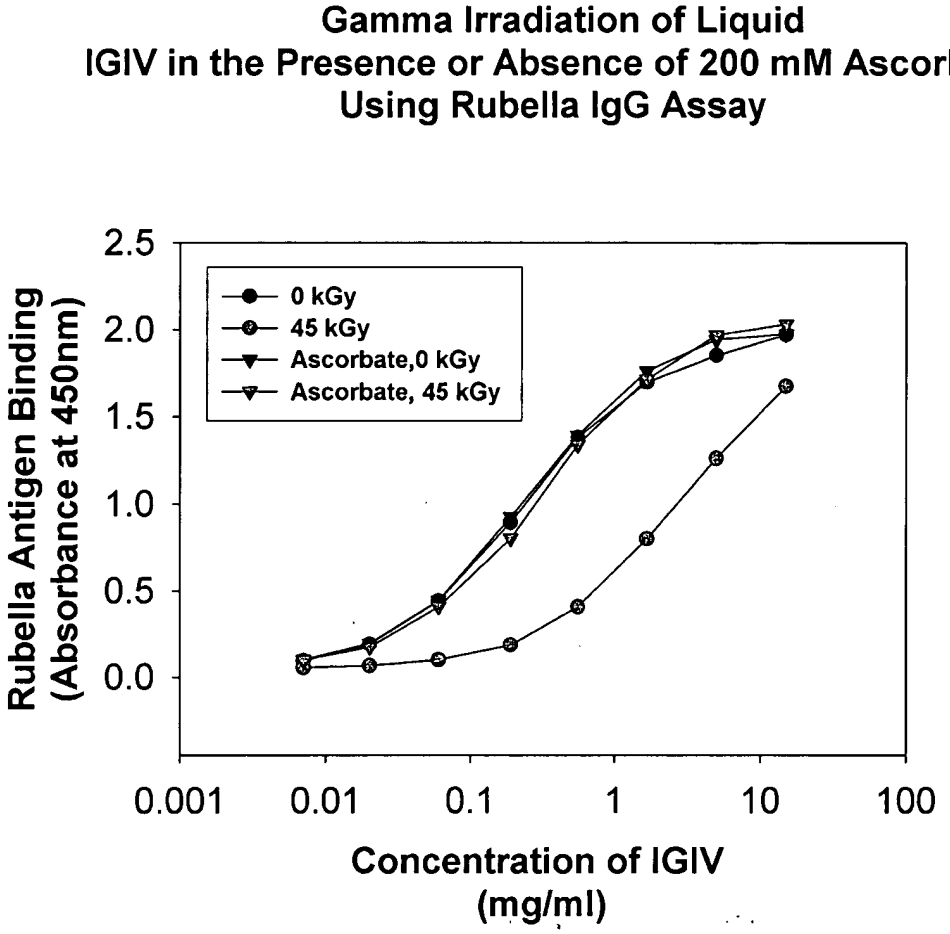
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate
Using Rubella IgG Assay
Rubella Antigen Binding
(Absorbance at 450nm)
2.5
2.0
1.5
1.0
0.5
0.0
0 kGy
45 kGy
Ascorbate,0 kGy
Ascorbate, 45 kGy
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3A

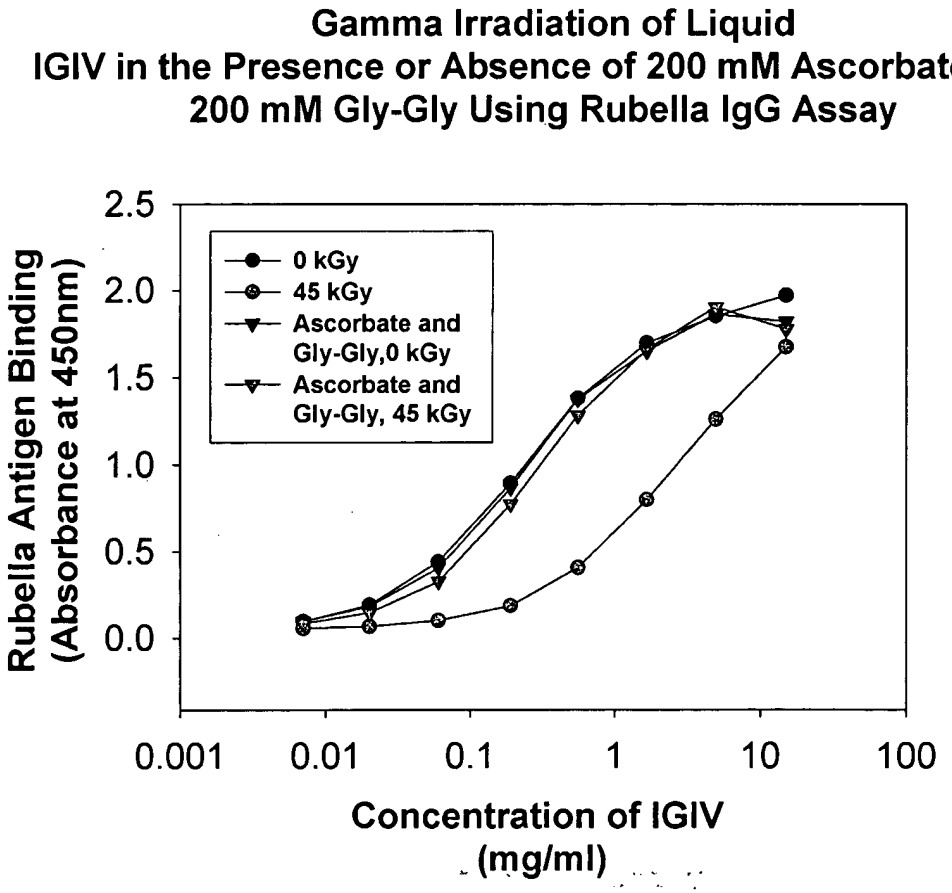
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate and
200 mM Gly-Gly Using Rubella IgG Assay
Rubella Antigen Binding
(Absorbance at 450nm)
2.5
2.0
1.5
1.0
0.5
0.0
0 kGy
45 kGy
Ascorbate and
Gly-Gly,0 kGy
Ascorbate and
Gly-Gly, 45 kGy
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3B

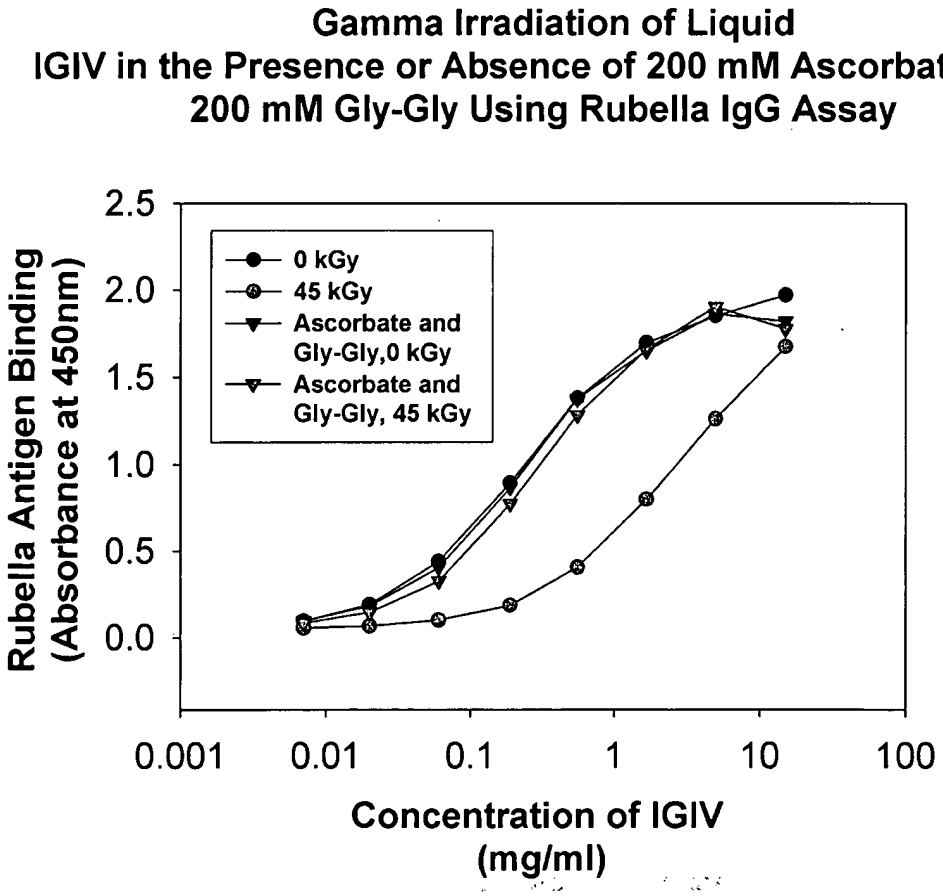
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate and
200 mM Gly-Gly Using Rubella IgG Assay
Rubella Antigen Binding
(Absorbance at 450nm)
2.5
2.0
1.5
1.0
0.5
0.0
0 kGy
45 kGy
Ascorbate and
Gly-Gly,0 kGy
Ascorbate and
Gly-Gly, 45 kGy
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3C

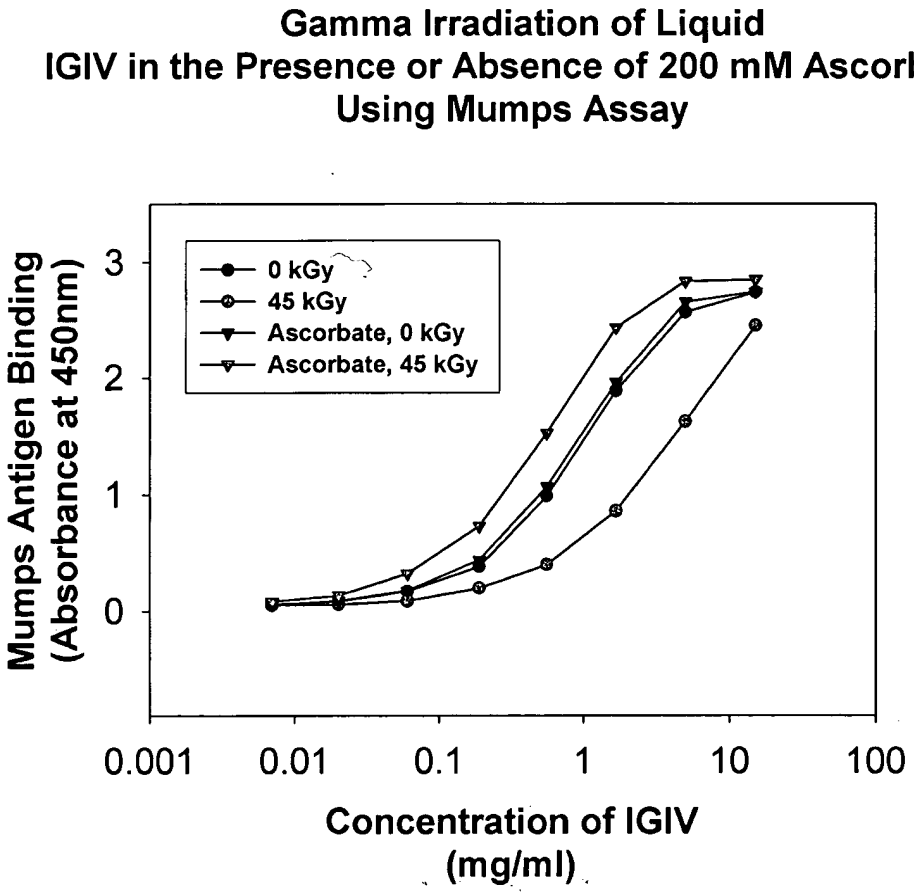
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate
Using Mumps Assay
Mumps Antigen Binding
(Absorbance at 450nm)
0 kGy
45 kGy
Ascorbate, 0 kGy
Ascorbate, 45 kGy
3
2
1
0
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3D

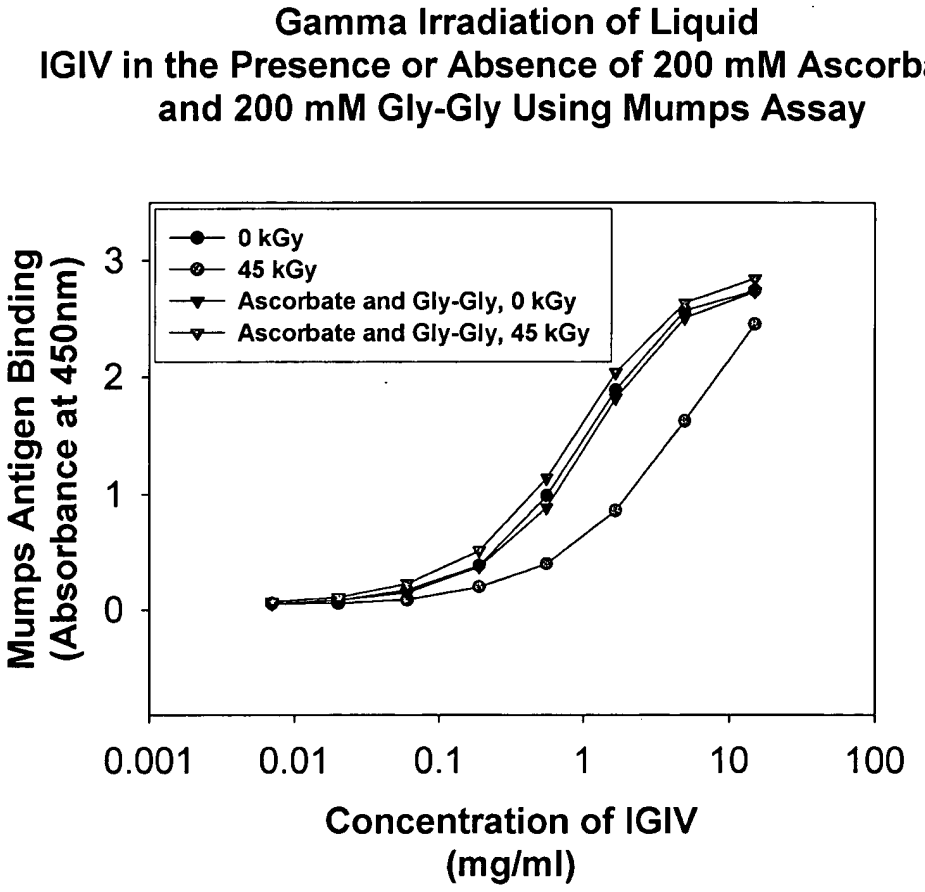
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate
and 200 mM Gly-Gly Using Mumps Assay
0 kGy
45 kGy
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 45 kGy
Mumps Antigen Binding
(Absorbance at 450nm)
3
2
1
0
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3E

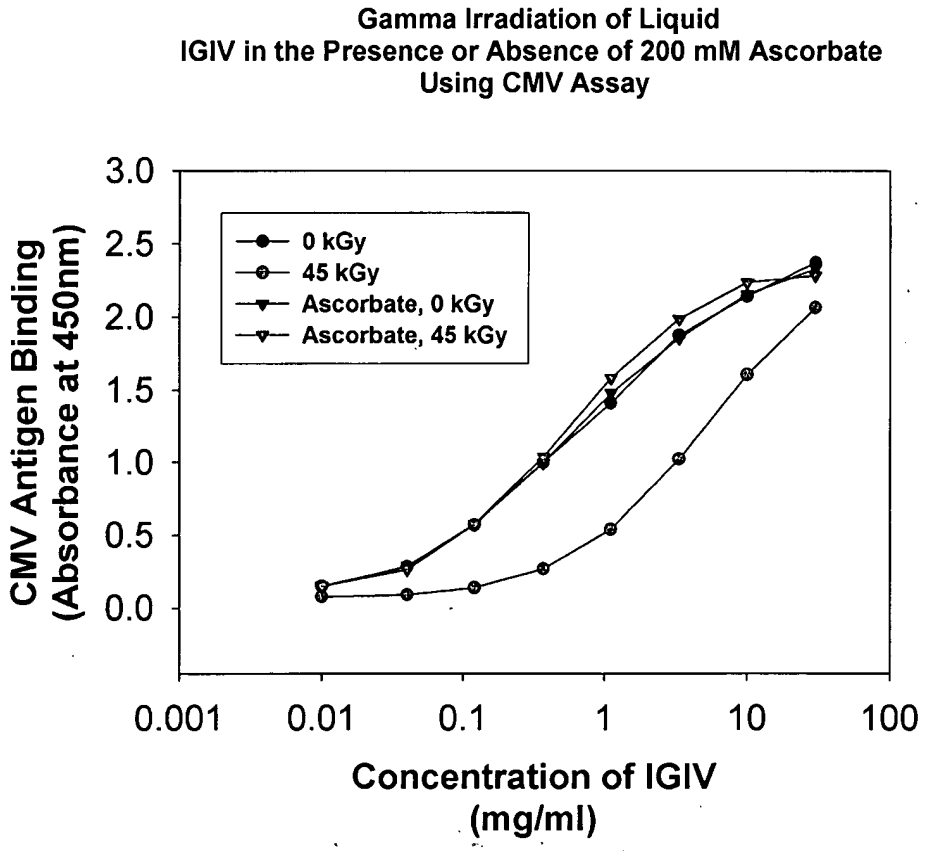
Gamma Irradiation of Liquid
IGIV in the Presence or Absence of 200 mM Ascorbate
Using CMV Assay
CMV Antigen Binding
(Absorbance at 450nm)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0 kGy
45 kGy
Ascorbate, 0 kGy
Ascorbate, 45 kGy
0.001
0.01
0.1
1
10
100
Concentration of IGIV
(mg/ml)

FIG. 3F

SDS-PAGE of Liquid IGIV

Liquid IGIV, Reduced 5-15%

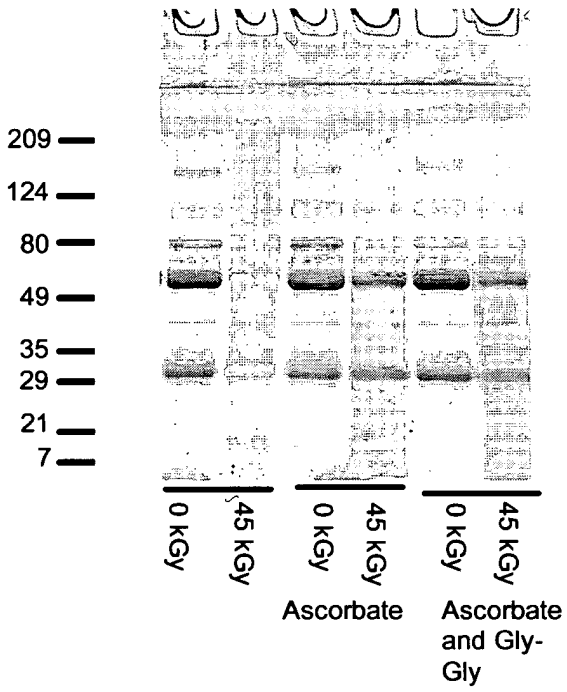

FIG. 3G

SDS-PAGE of Liquid IGIV

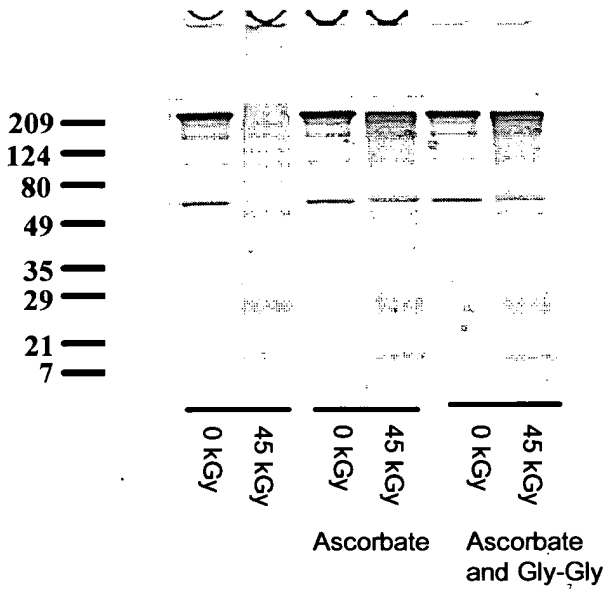

FIG. 3H

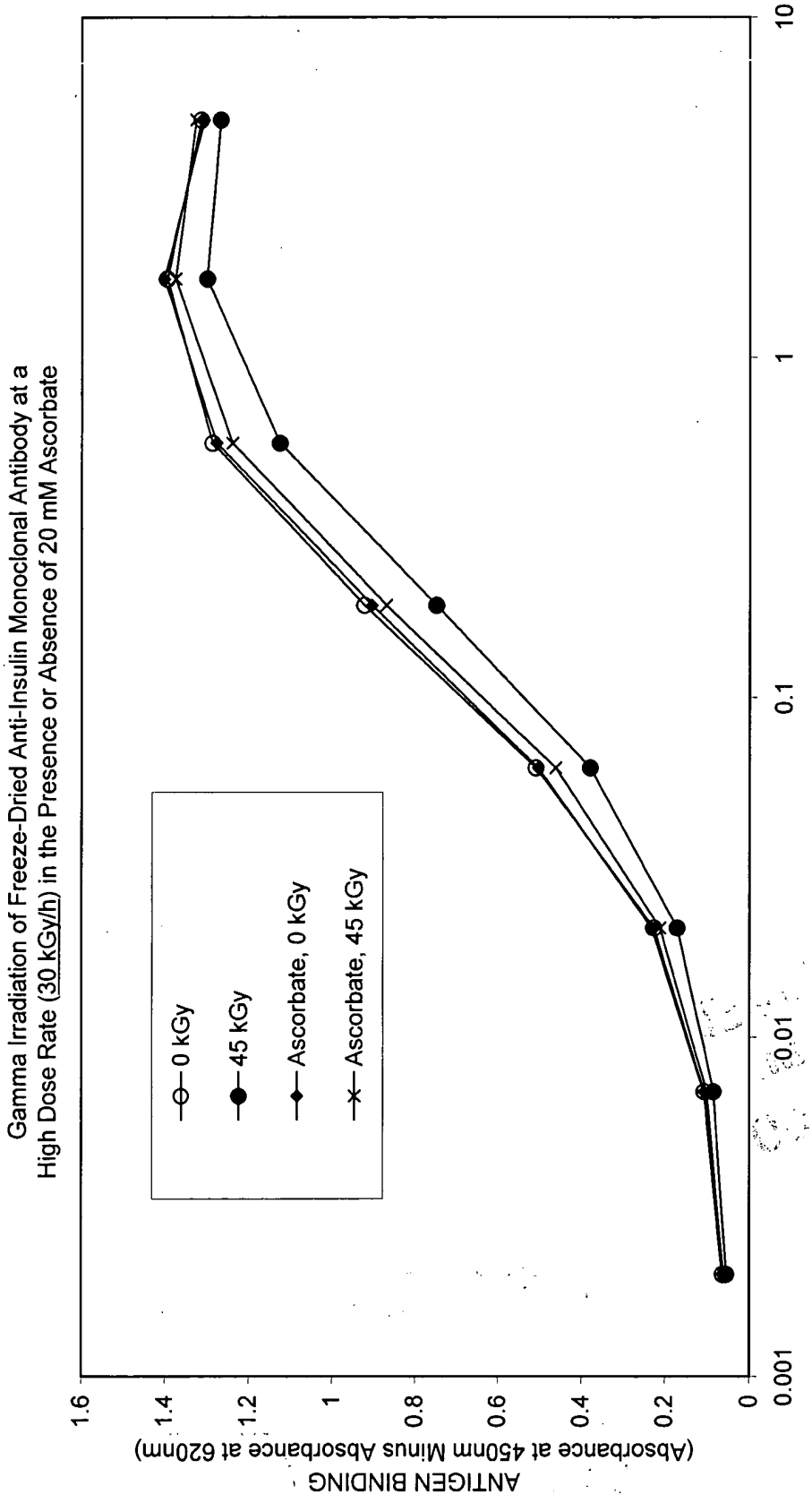
Gamma Irradiation of Freeze-Dried Anti-Insulin Monoclonal Antibody at a
High Dose Rate (30 kGy/h) in the Presence or Absence of 20 mM Ascorbate
ANTIGEN BINDING
(Absorbance at 450nm Minus Absorbance at 620nm)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.001
0.01
0.1
1
10
Concentration of Anti-Insulin Monoclonal Antibody
(µg/ml)
0 kGy
45 kGy
Ascorbate, 0 kGy
Ascorbate, 45 kGy

FIG. 4A

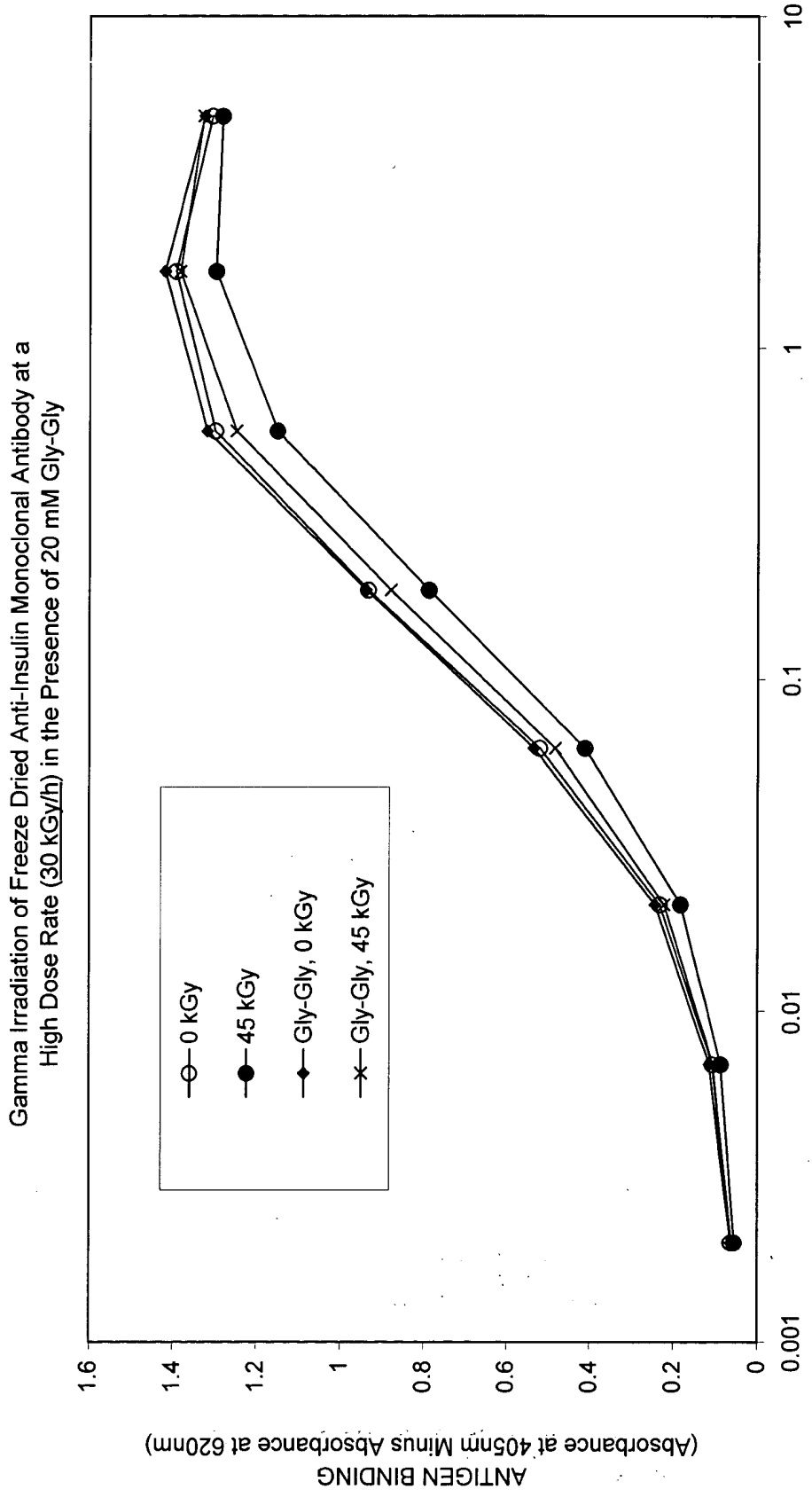
Gamma Irradiation of Freeze Dried Anti-Insulin Monoclonal Antibody at a
High Dose Rate (30 kGy/h) in the Presence of 20 mM Gly-Gly
ANTIGEN BINDING
(Absorbance at 405nm Minus Absorbance at 620nm)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.001
0.01
0.1
1
10
Concentration of Anti-Insulin Monoclonal Antibody
(µg/ml)
0 kGy
45 kGy
Gly-Gly, 0 kGy
Gly-Gly, 45 kGy

FIG. 4B

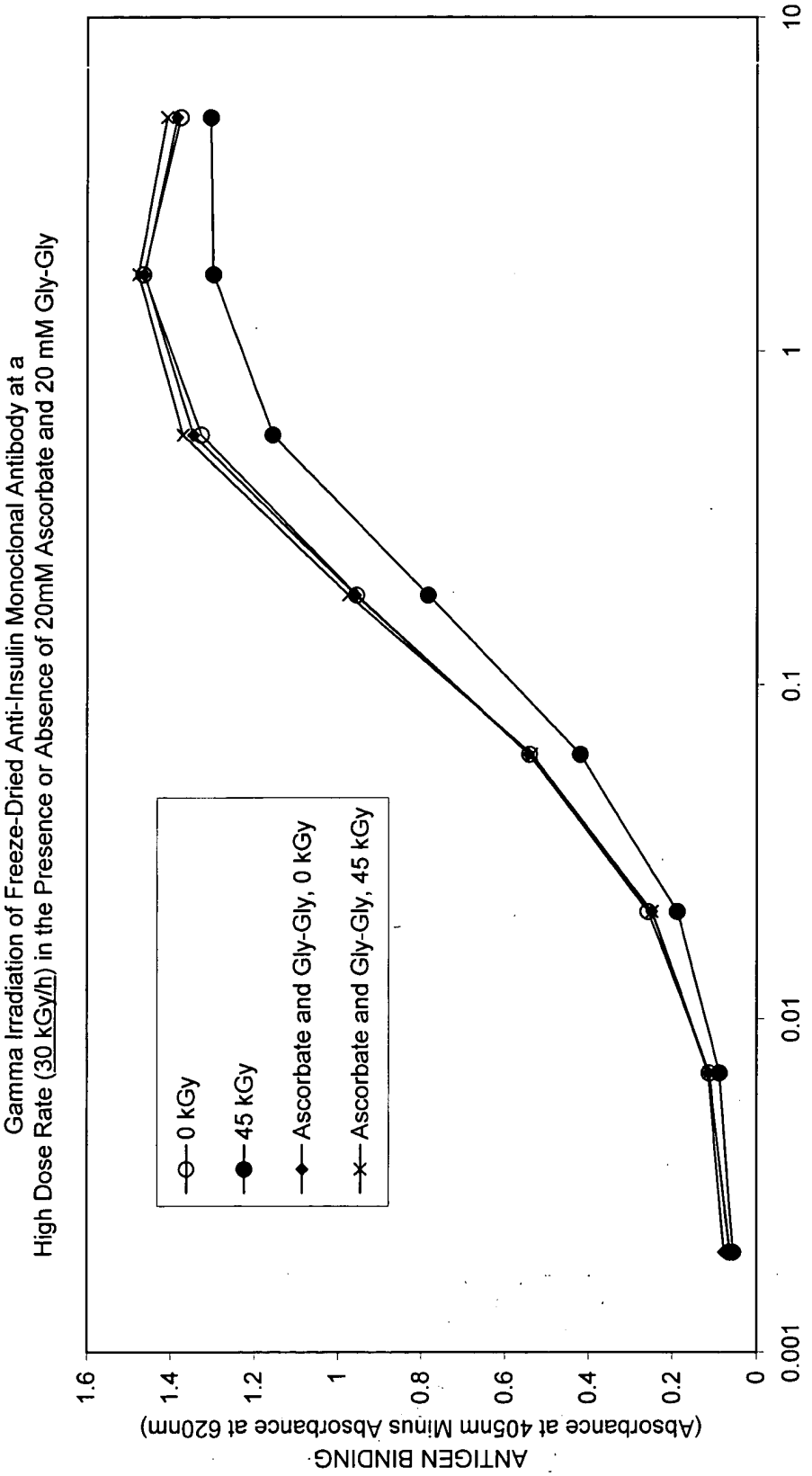
Gamma Irradiation of Freeze-Dried Anti-Insulin Monoclonal Antibody at a
High Dose Rate (30 kGy/h) in the Presence or Absence of 20mM Ascorbate and 20 mM Gly-Gly
ANTIGEN BINDING
(Absorbance at 405nm Minus Absorbance at 620nm)
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
0.001
0.01
0.1
1
10
Concentration of Anti-Ig Lambda Light Chain
(µg/ml)
0 kGy
45 kGy
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 45 kGy

FIG. 4C

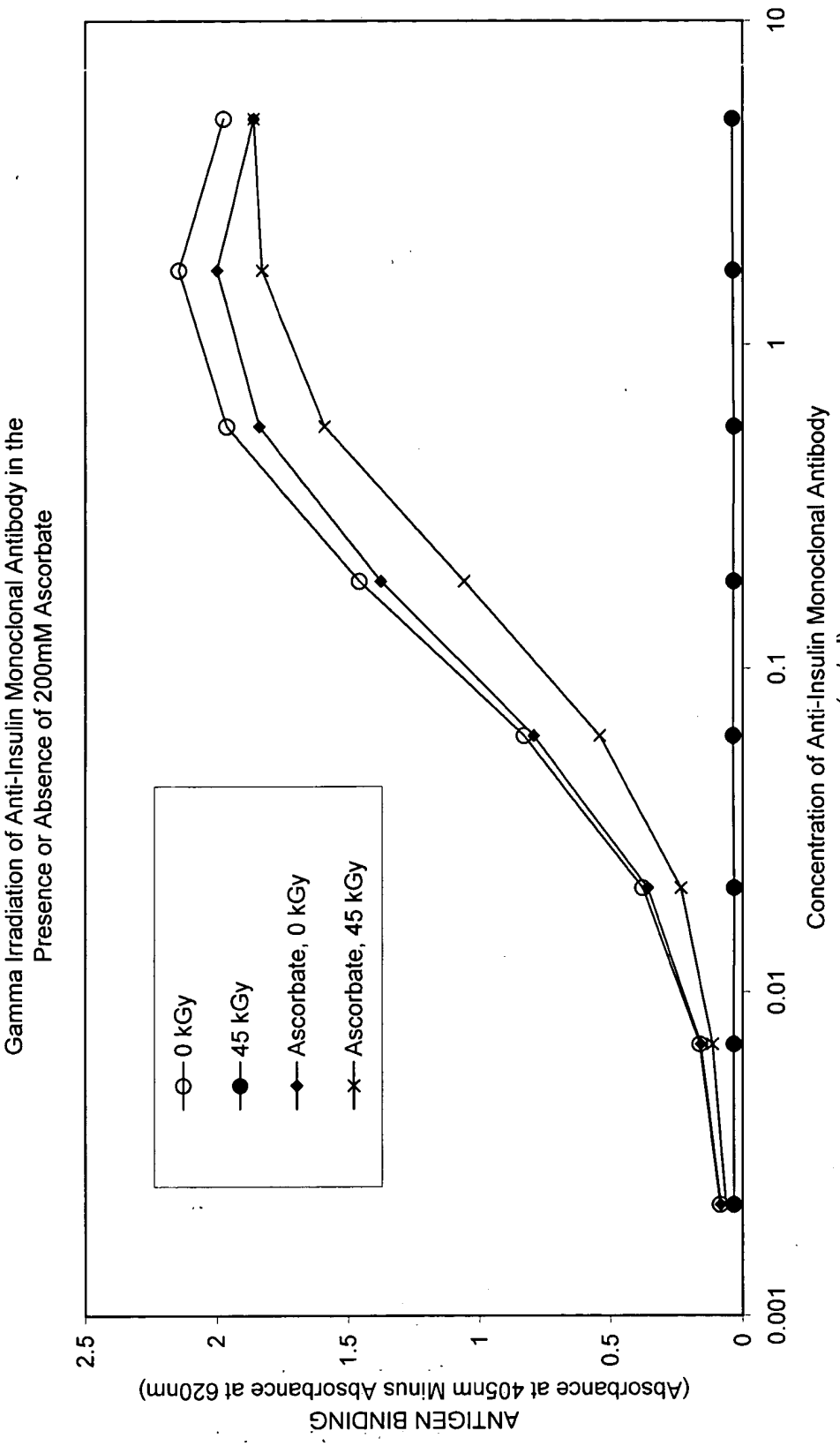
Gamma Irradiation of Anti-Insulin Monoclonal Antibody in the Presence or Absence of 200mM Ascorbate
ANTIGEN BINDING
(Absorbance at 405nm Minus Absorbance at 620nm)
2.5
2
1.5
1
0.5
0
0.001
0.01
0.1
1
10
Concentration of Anti-Insulin Monoclonal Antibody (µg/ml)
0 kGy
45 kGy
Ascorbate, 0 kGy
Ascorbate, 45 kGy

FIG. 5A

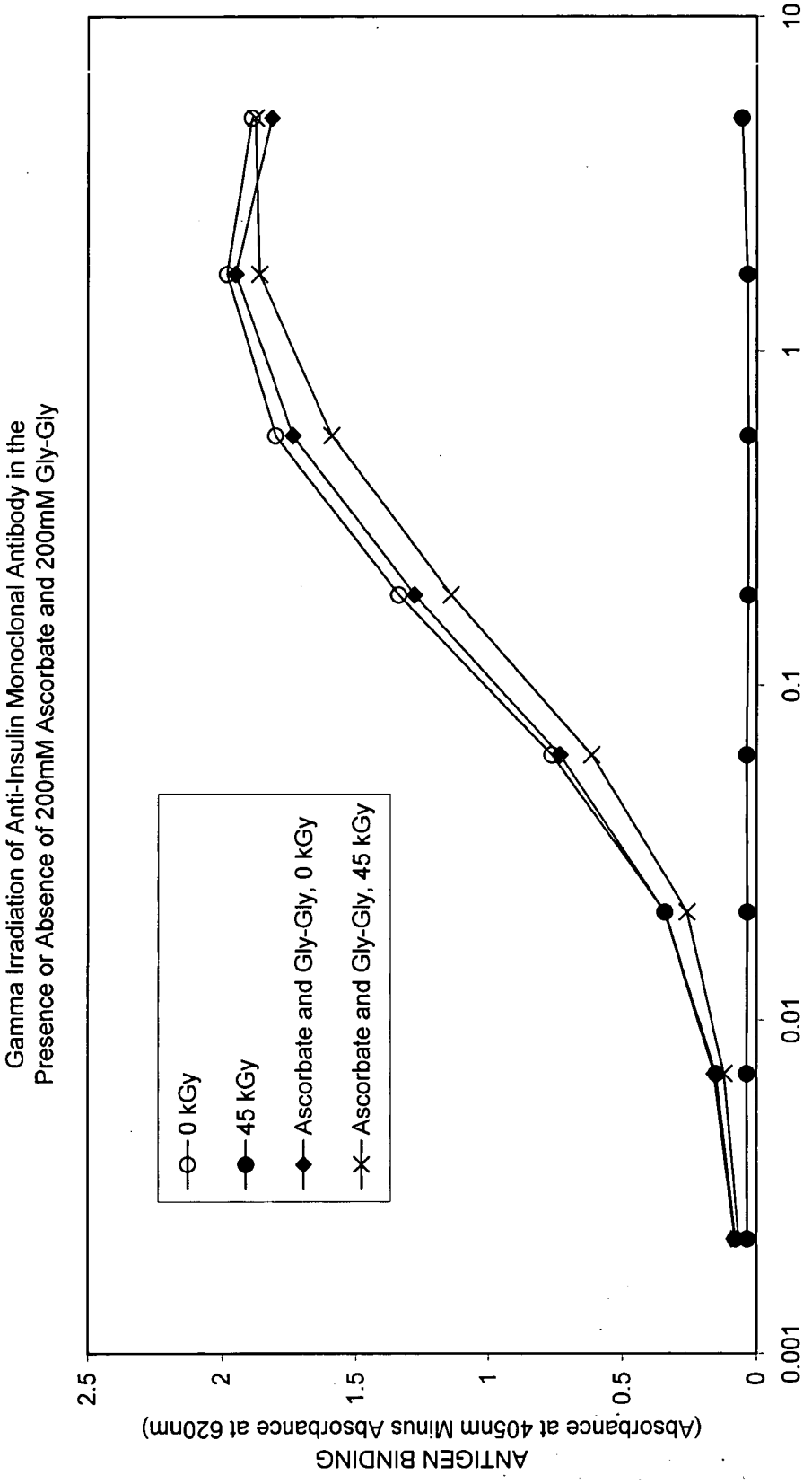
Gamma Irradiation of Anti-Insulin Monoclonal Antibody in the Presence or Absence of 200mM Ascorbate and 200mM Gly-Gly
ANTIGEN BINDING
(Absorbance at 405nm Minus Absorbance at 620nm)
2.5
2
1.5
1
0.5
0
0.001
0.01
0.1
1
10
Concentration of Anti-Insulin Monoclonal Antibody (µg/ml)
0 kGy
45 kGy
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 45 kGy

FIG. 5B

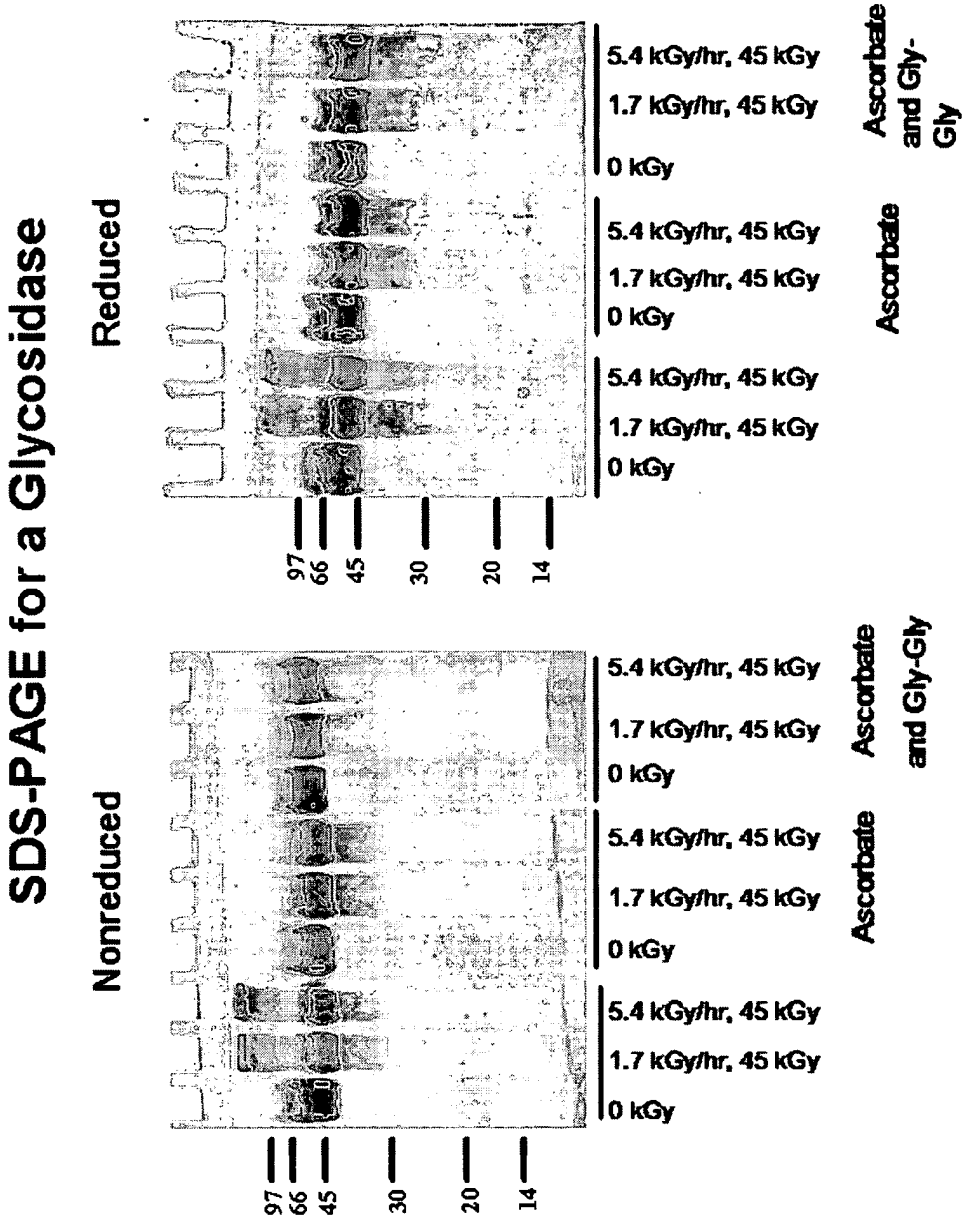
SDS-PAGE for a Glycosidase
Reduced
Nonreduced
5.4 kGy/hr, 45 kGy
1.7 kGy/hr, 45 kGy
0 kGy
Ascorbate and Gly-Gly
Ascorbate
97
66
45
30
20
14

FIG. 6A

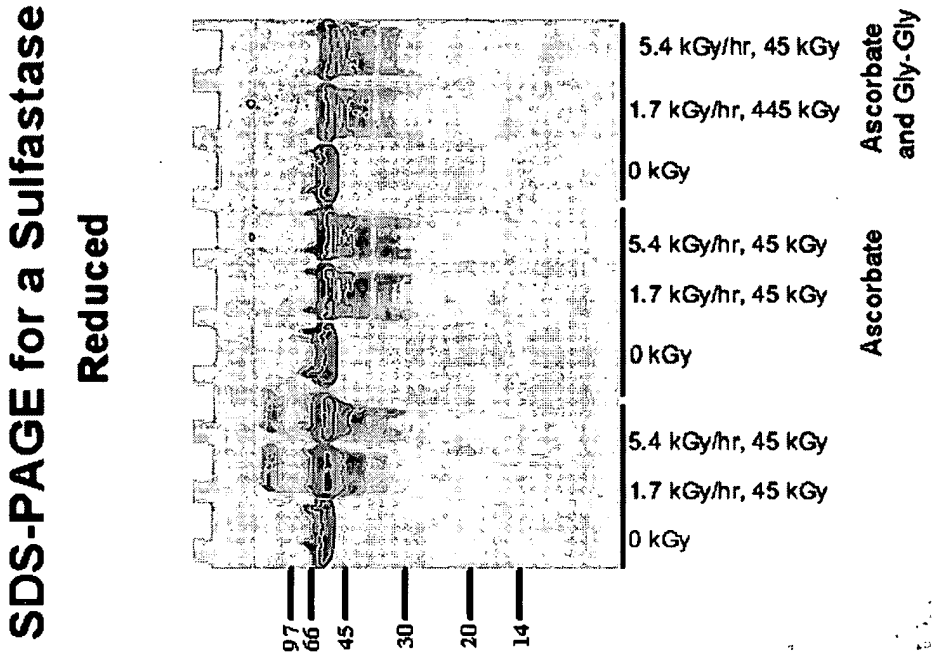
SDS-PAGE for a Sulfastase
Reduced
97
66
45
30
20
14
5.4 kGy/hr, 45 kGy
1.7 kGy/hr, 445 kGy
0 kGy
Ascorbate and Gly-Gly
5.4 kGy/hr, 45 kGy
1.7 kGy/hr, 45 kGy
0 kGy
Ascorbate
5.4 kGy/hr, 45 kGy
1.7 kGy/hr, 45 kGy
0 kGy

FIG. 6B

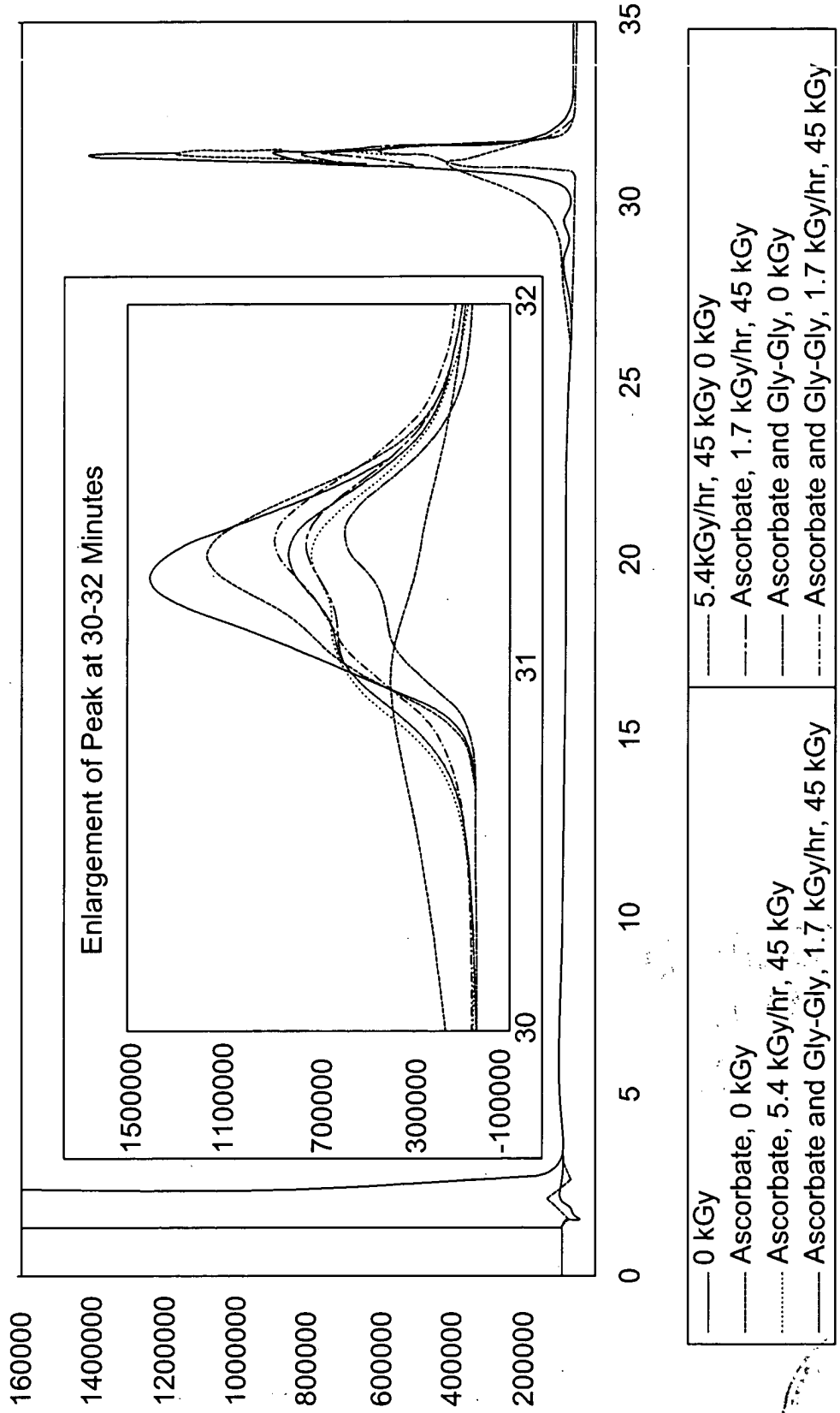
Gamma Irradiation of a Glycosidase In the Presence or Absence of Ascorbate Alone or in Combination with Gly-Gly
mVolts
160000
1400000
1200000
1000000
800000
600000
400000
200000
0
5
10
15
20
25
30
35
Enlargement of Peak at 30-32 Minutes
1500000
1100000
700000
300000
-100000
30
31
32
0 kGy
Ascorbate, 0 kGy
Ascorbate, 5.4 kGy/hr, 45 kGy
Ascorbate and Gly-Gly, 1.7 kGy/hr, 45 kGy
5.4kGy/hr, 45 kGy 0 kGy
Ascorbate, 1.7 kGy/hr, 45 kGy
Ascorbate and Gly-Gly, 0 kGy
Ascorbate and Gly-Gly, 1.7 kGy/hr, 45 kGy

FIG. 7

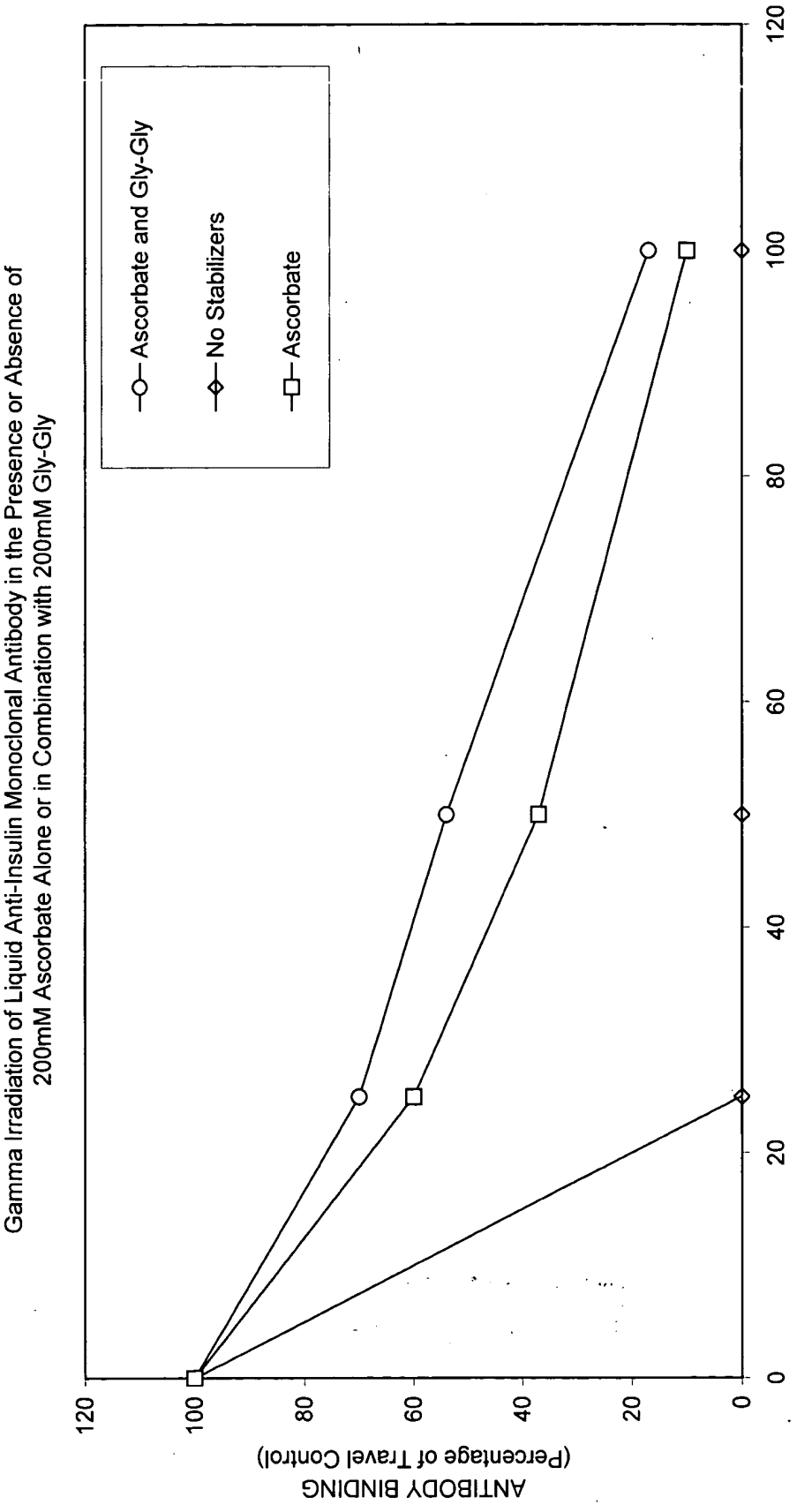
Gamma Irradiation of Liquid Anti-Insulin Monoclonal Antibody in the Presence or Absence of 200mM Ascorbate Alone or in Combination with 200mM Gly-Gly
Ascorbate and Gly-Gly
No Stabilizers
Ascorbate
ANTIBODY BINDING
(Percentage of Travel Control)
Total Dose
(kGy)
0
20
40
60
80
100
120

FIG. 8

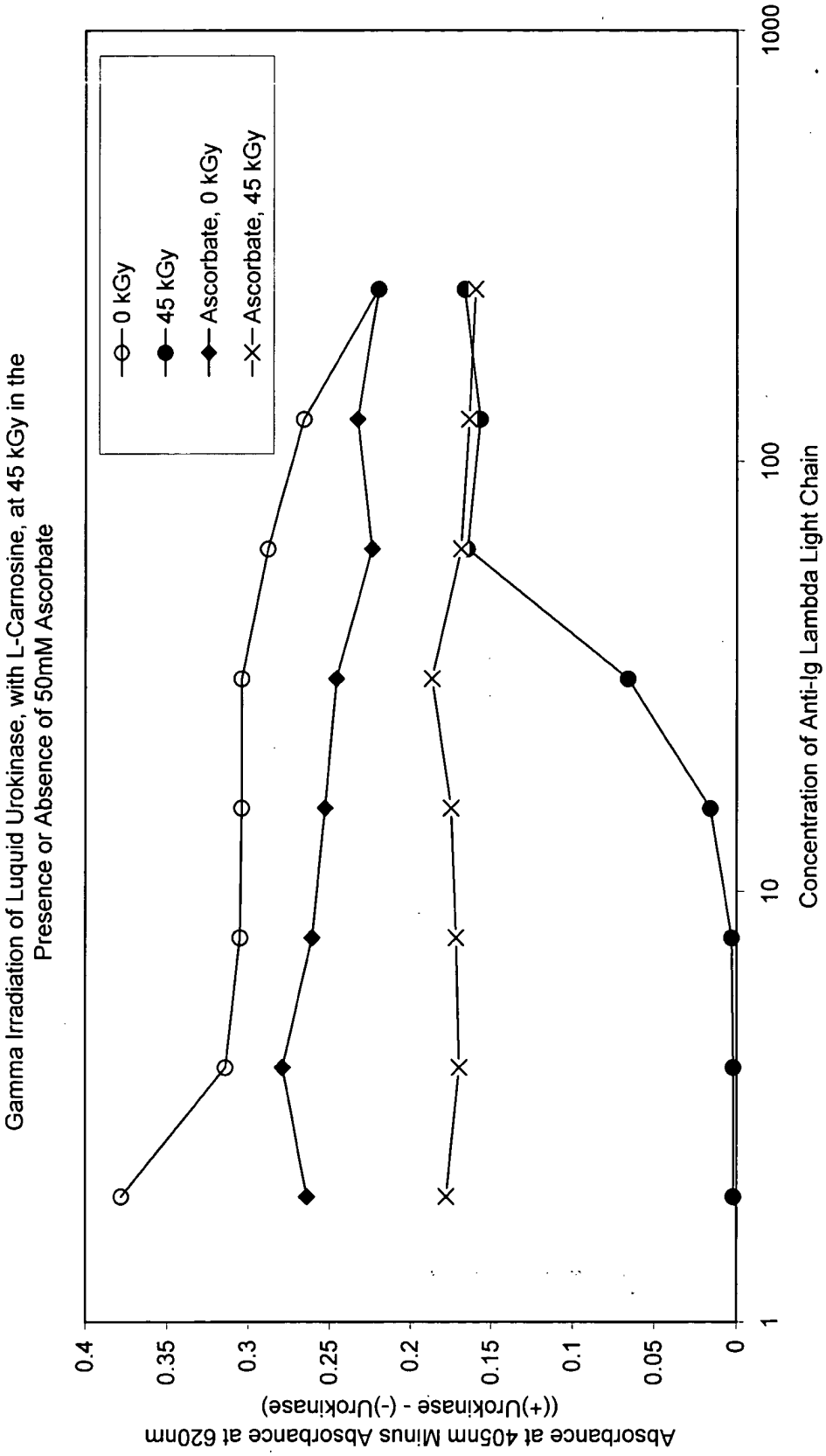
Gamma Irradiation of Luquid Urokinase, with L-Carnosine, at 45 kGy in the Presence or Absence of 50mM Ascorbate
0 kGy
45 kGy
Ascorbate, 0 kGy
Ascorbate, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm ((+)Urokinase - (-)Urokinase)
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
1
10
100
1000
Concentration of Anti-Ig Lambda Light Chain (mM)

FIG. 9

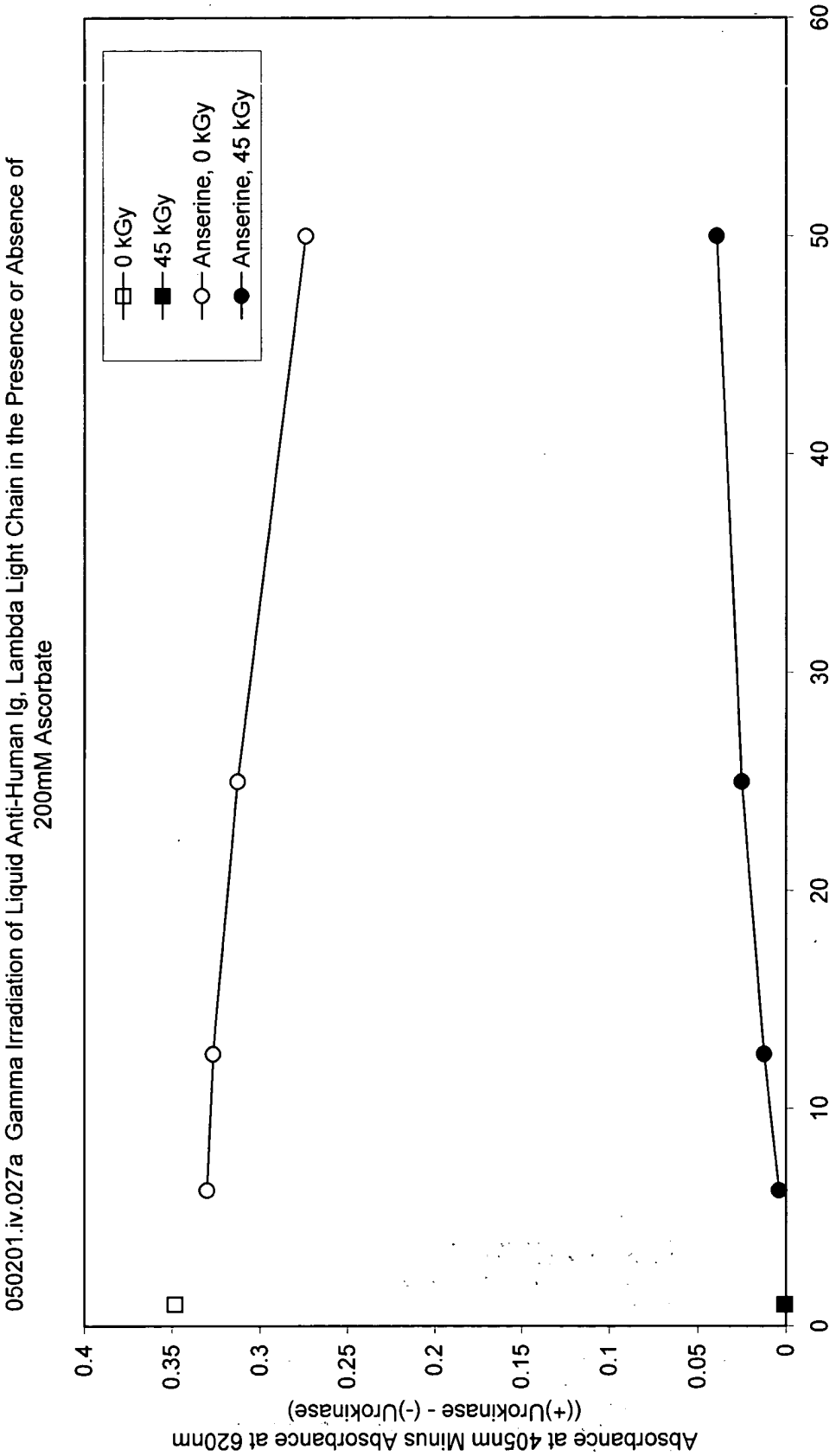
050201.iv.027a Gamma Irradiation of Liquid Anti-Human Ig, Lambda Light Chain in the Presence or Absence of 200mM Ascorbate
0 kGy
45 kGy
Anserine, 0 kGy
Anserine, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm
((+)Urokinase - (-)Urokinase)
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
10
20
30
40
50
60
Concentration of Anserine
(mM)

FIG. 10

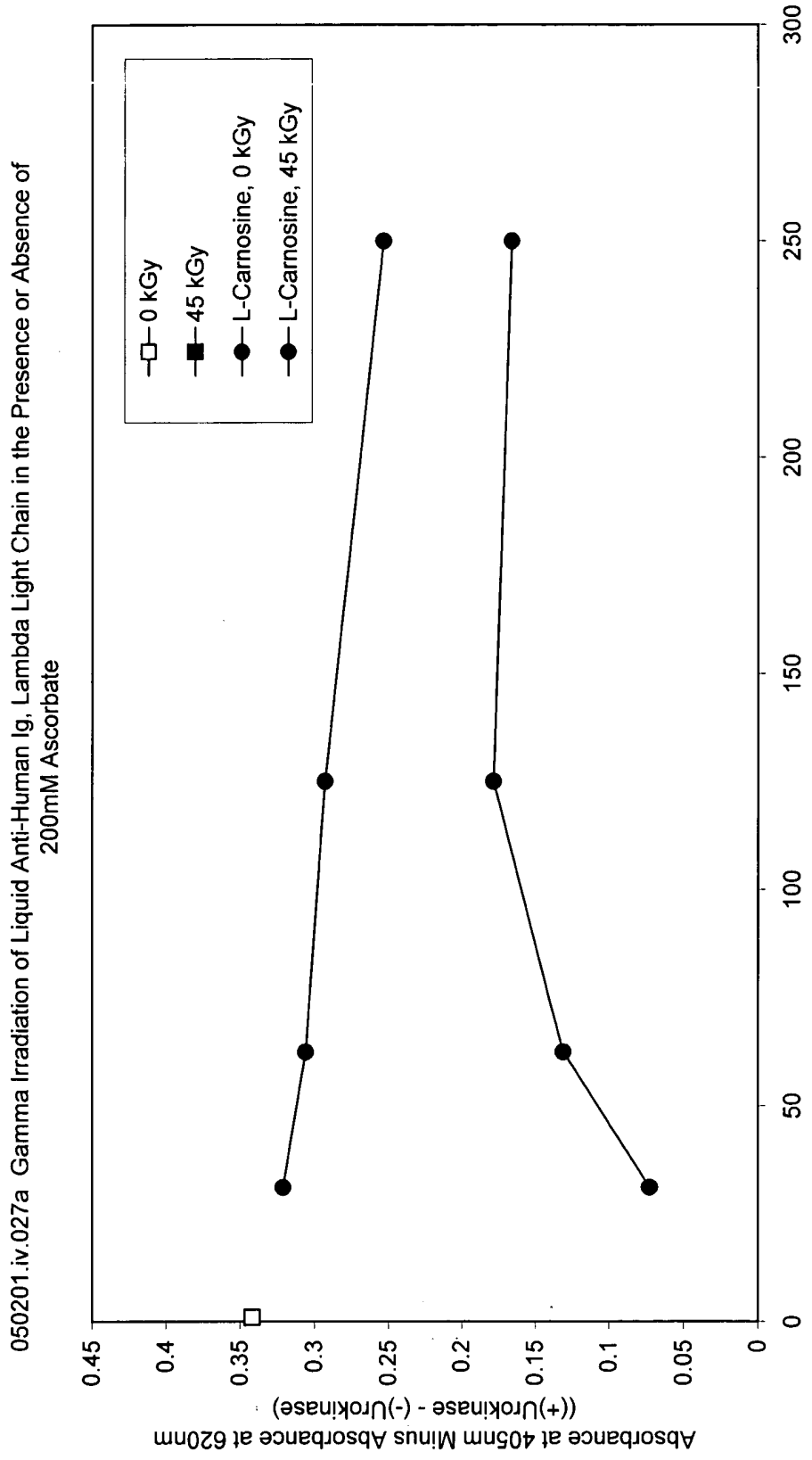
050201.iv.027a Gamma Irradiation of Liquid Anti-Human Ig, Lambda Light Chain in the Presence or Absence of 200mM Ascorbate
0 kGy
45 kGy
L-Carnosine, 0 kGy
L-Carnosine, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm ((+)Urokinase - (-)Urokinase)
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
0
50
100
150
200
250
300
Concentration of Anti-Ig Lambda Light Chain (mM)

FIG. 11

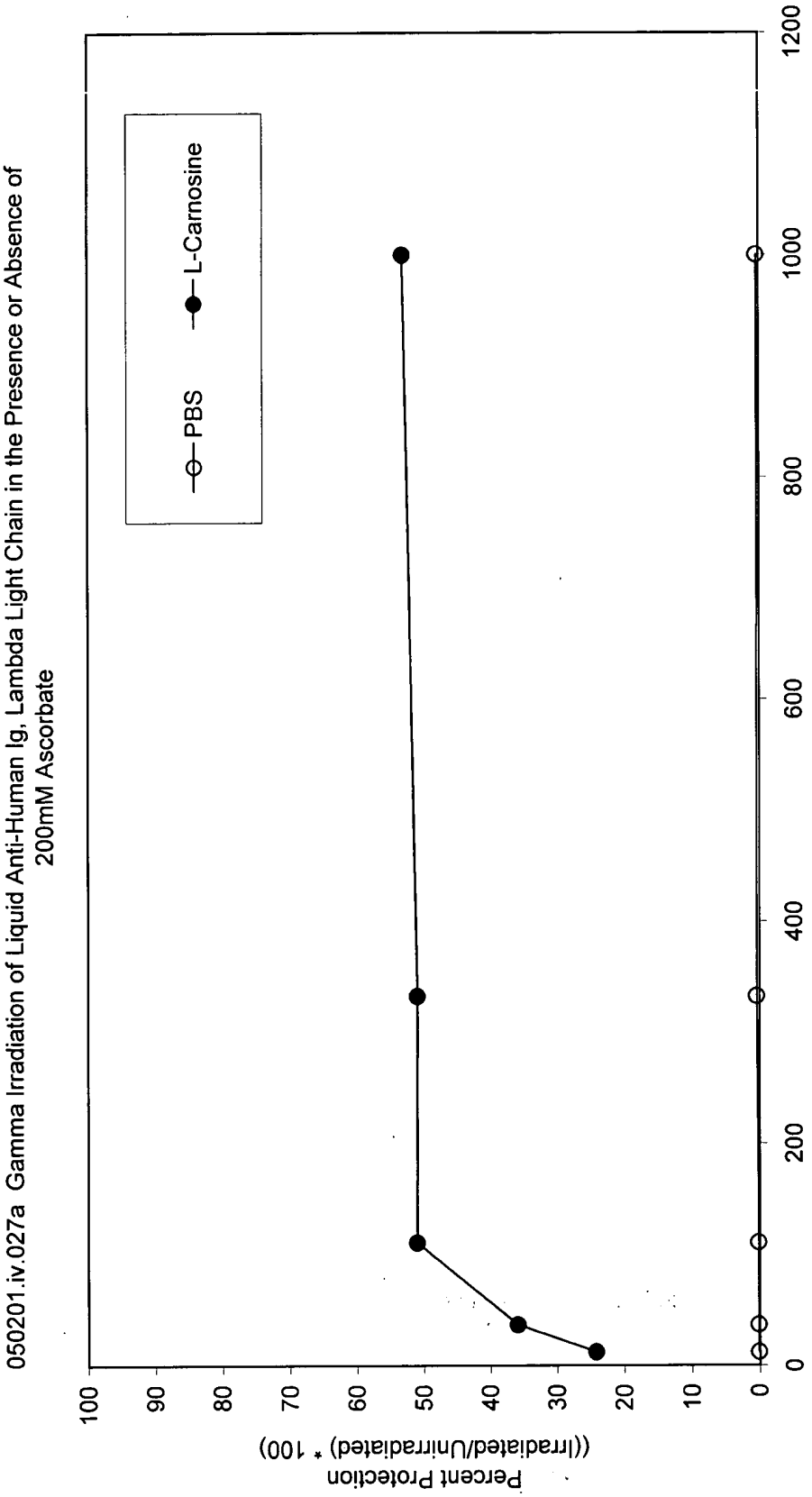
050201.iv.027a Gamma Irradiation of Liquid Anti-Human Ig, Lambda Light Chain in the Presence or Absence of 200mM Ascorbate
PBS
L-Carnosine
Percent Protection ((Irradiated/Unirradiated) * 100)
Concentration of Anti-Ig Lambda Light Chain (µg/ml)
0
10
20
30
40
50
60
70
80
90
100
0
200
400
600
800
1000
1200

FIG. 12

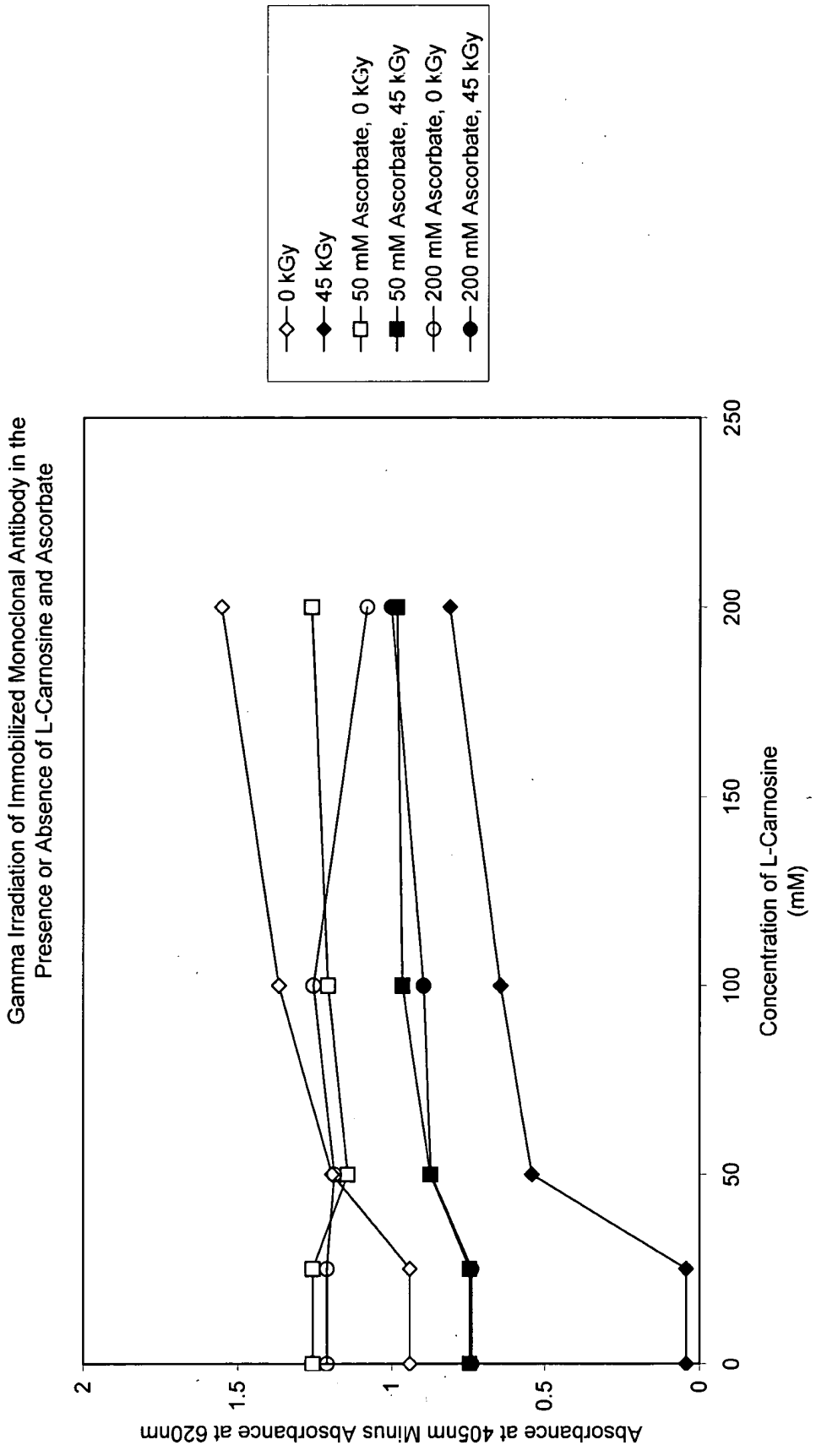
Gamma Irradiation of Immobilized Monoclonal Antibody in the Presence or Absence of L-Carnosine and Ascorbate
0 kGy
45 kGy
50 mM Ascorbate, 0 kGy
50 mM Ascorbate, 45 kGy
200 mM Ascorbate, 0 kGy
200 mM Ascorbate, 45 kGy
Absorbance at 405nm Minus Absorbance at 620nm
0
0.5
1
1.5
2
Concentration of L-Carnosine (mM)
0
50
100
150
200
250

FIG. 13

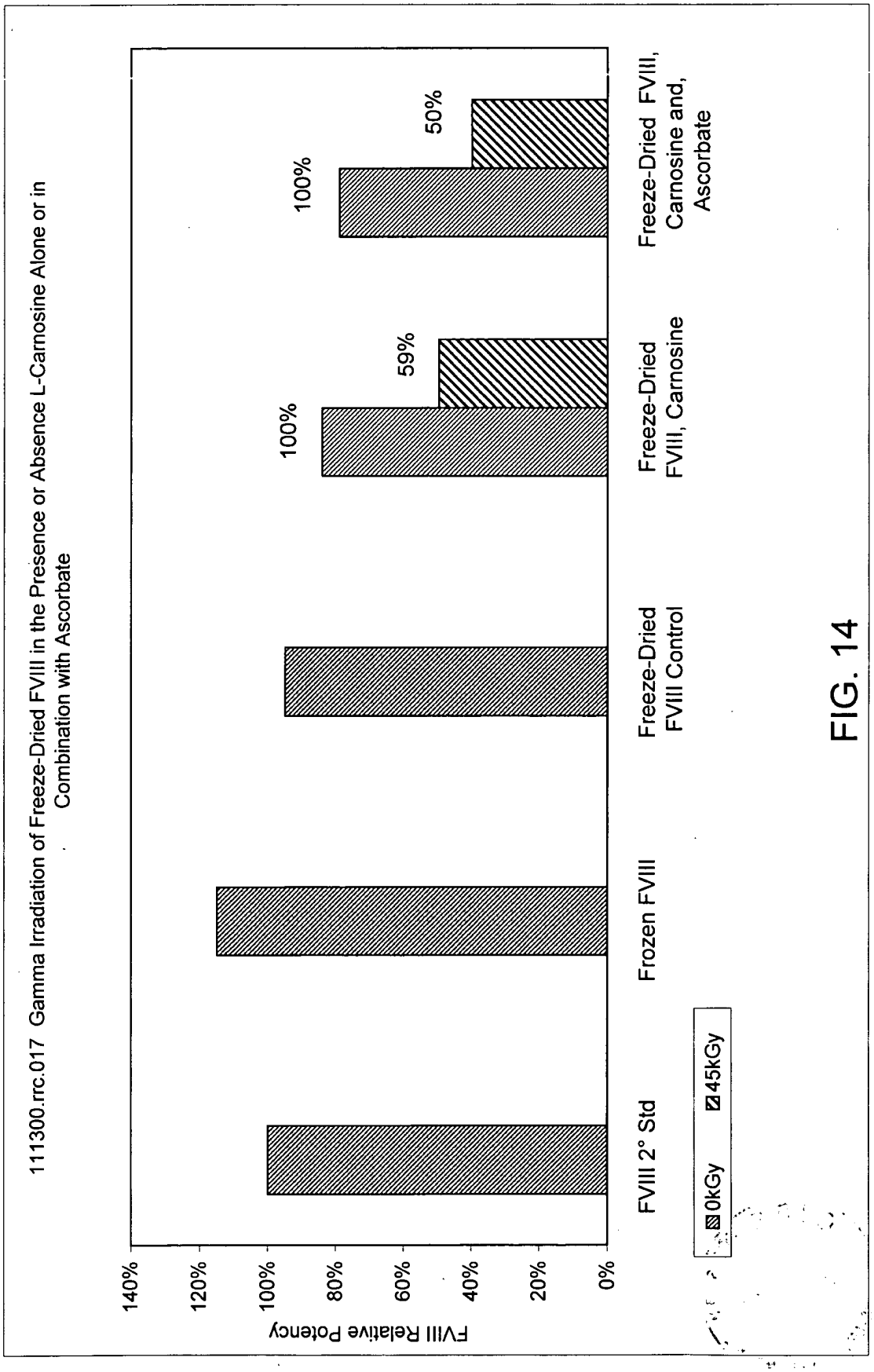
111300.rrc.017 Gamma Irradiation of Freeze-Dried FVIII in the Presence or Absence L-Carnosine Alone or in Combination with Ascorbate
FVIII Relative Potency
140%
120%
100%
80%
60%
40%
20%
0%
100%
100%
59%
100%
50%
FVIII 2° Std
Frozen FVIII
Freeze-Dried FVIII Control
Freeze-Dried FVIII, Carnosine
Freeze-Dried FVIII, Carnosine and, Ascorbate
0kGy
45kGy

FIG. 14